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**DOES NOT CONTAIN CBI**

SEHSC®
SILICONES ENVIRONMENTAL, HEALTH AND SAFETY COUNCIL NORTH AMERICA

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TSCA Confidential Business Information Center (7407M)
EPA East – Room 6428
Attn: Section 8(e)
U.S. Environmental Protection Agency
Ariel Rios Building
1200 Pennsylvania Avenue, NW
Washington, DC 20460-0001

Re: Supplemental TSCA Section 8(e) Submission; Final Report - Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test for Dimethylsilanediol in Sprague-Dawley Rats via Oral Gavage – 8EHQ-09-17359

Dear TSCA Section 8(e) Coordinator:

In accordance with the provisions of Section 8(e) of the Toxic Substances and Control Act (TSCA), as interpreted in the TSCA Section 8(e) Policy Statement and Guidance, Fed. Reg. 33129 (June 3, 2003) and other Agency guidance, the Silicones Environmental, Health and Safety Council (SEHSC)[1] submits, on behalf of its member companies, the following information as a supplemental submission to our December 19, 2008 TSCA Section 8(e) notification. Our initial notification reported the preliminary results of the referenced study. This supplemental submission provides the final report. Neither SEHSC, nor any member company, has made a determination at this time that any significant risk of injury to human health or the environment is presented by these findings.

**Chemical Substance**

1066-42-8 Dimethylsilanediol

**Final Study Report**

Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test for Dimethylsilanediol in Sprague-Dawley Rats via Oral Gavage. This study design is based on the USEPA OPPTS 870.3650 and OECD 422 test guidelines that include a neurotoxicity screening assessment.

[1] SEHSC is a not-for-profit trade association whose mission is to promote the safe use of silicones through product stewardship and environmental, health, and safety research. The Council is comprised of North American silicone chemical producers and importers.

CONTAINS NO CBI

322101

**Study Summary**

The objective of this study was to evaluate the potential toxicity of dimethylsilanediol in a 28-day combined repeated dose toxicity study with the reproductive/developmental toxicity screening test in Sprague-Dawley rats by oral gavage administration based on OECD Test Guideline number 422. The test substance was administered by oral gavage in corn oil for 28 days (toxicity group females) or 29 days (males) to 10 rats/sex/group (the toxicity group females at 50 mg/kg bw group where N=9) at 0, 50, 250 or 500 mg/kg bw/day. A single group of males was used for both the toxicity and reproductive phases of the study. Ten reproductive group females per dose group were treated for 14 days prior to the mating period, during the mating period and through post-partum day 3.

Animals were observed twice daily on weekdays and once daily on weekends and holidays for mortality or morbidity. Clinical observations were performed daily immediately following exposure. Body weight measurements were performed weekly. All animals received a detailed physical examination once before the first dose to allow for within-subject comparisons, and weekly thereafter. Additional body weights were obtained for reproductive females on gestational days (GD) 0, 7, 14, and 20, within 24 hours of parturition, and on post-partum day four. Individual food consumption was recorded at least weekly, except during the cohabitation period. Functional observational battery (FOB) and motor activity evaluations were performed on males and toxicity group females once prior to initiation of exposures and during the 4th week of exposure. Blood samples for hematology and serum chemistry evaluations were collected at the scheduled necropsy from males and toxicity group females. Complete necropsies were performed on the males and the toxicity group females and selected organs were weighed. Microscopic examination was performed on protocol-specified tissues on all toxicity group animals from the control and 500 mg/kg bw/day dose groups. Target tissues examined from the 50 and 250 mg/kg bw/day groups included liver, lung, prostate gland and thyroid gland from male rats and liver and lung from toxicity group females.

Mating was initiated after the first two weeks of exposure by pairing reproductive group females with males of the same treatment group until positive evidence of mating was obtained. Reproductive and developmental parameters evaluated included evidence of mating, pregnancy, duration of gestation, mean litter size, mean live litter size, mean litter weight, and mean ratio of live births/litter size. Dams and pups were euthanized on post-partum day 4 and examined for external gross lesions. The number of corpora lutea, and the number of uterine implantation sites were determined for all reproductive group females.

Oral gavage administration of dimethylsilanediol to male and female Sprague-Dawley rats at concentrations of up to 500 mg/kg bw/day was generally well tolerated by males and females. For males at 250 and 500 mg/kg bw/day significant soiling was observed (abdominal region and urogenital soiling). Soiling of the muzzle was a significant observation in the toxicity group females at 500 mg/kg bw/day. Both abdominal soiling and urogenital soiling were significant observations in the reproductive group females at 500 mg/kg bw/day.

There were no statistically significant differences in the mean body weights on any day for males, toxicity group females and reproductive group females. With respect to body weight gain, 500 mg/kg bw/day males had a significant decrease in body weight gain during week 4 (45%) and in total gain from day 1 to 29 (23%). For 500 mg/kg bw/day toxicity group females, there was significant decrease in body weight gain during week 3 (49%). There were no statistically significant differences in body

weight gain for the reproductive group females in any of the treatment groups during any of the measured intervals.

There were no differences in the average daily food consumption between control and any treatment groups for any of the measured time periods.

There were no significant differences of toxicological significance between the control and treatment groups in either sex for the FOB ranked tests, FOB continuous tests and motor activity. There were no treatment-related changes associated with dimethylsilanediol administration on rat neurobiological function as evaluated with FOB and motor activity parameters.

Statistically identified differences in clinical pathology and hematology were not considered toxicologically significant since the findings were within or slightly below historical control ranges for this laboratory and the findings did not correlate with a pathological outcome.

The statistically significant increase in liver weights in males and toxicity group females at 250 and 500 mg/kg bw/day correlated with the histopathologic finding of centrilobular hypertrophy. There were no other treatment-related differences in organ weights (absolute and relative) for males and toxicity group females.

A standard set of protocol-defined tissues was examined for control and high-dose groups. Suspected target tissues were examined for 50 and 250 mg/kg bw/day groups. There were three primary effects of the test article observed in the liver, including centrilobular hypertrophy in both sexes, periportal hepatocellular vacuolation (microvesicular lipidosis, females only), and hepatic porphyria[2] (males only) which was accompanied by chronic inflammation and bile duct hyperplasia. Centrilobular hypertrophy is considered an adaptive change. Hepatic lipidosis, unless severe, is generally considered non-adverse. Follicular cell hypertrophy was observed in the thyroid gland of 250 and 500 mg/kg bw/day male rats. This may reflect an adaptive secondary effect and may be considered to be adverse in the rat, but the mechanism of action is generally not applicable to species such as humans with significant levels of thyroid binding globulin (Capen, *et al.,* 2002).

There were no treatment-related effects apparent for any of the reproductive endpoints: gestation length, litter size, litter weight, ratio live births/litter size, litter sex ratio, number of implantation sites, number of corpora lutea, post-implantation loss, mating and fertility indices.

Based on hepatic porphyria in males and hepatic microvesicular lipidosis in toxicity group females observed in this study, the systemic toxicity NOAEL (No-Observed-Adverse-Effect-Level) for dimethylsilanediol in rats via oral administration in corn oil is considered to be 250 mg/kg bw/day for male rats and toxicity group female rats. In the absence of adverse effects on reproductive or developmental parameters in this study, a NOAEL of 500 mg/kg bw/day is assigned for both reproductive and developmental toxicity.

**Attachment**

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[2] Also referred to as *protoporphyrinosis*. *Porphyria (or protoporphyrinosis)* refers to disorders characterized by the buildup of precursors of heme (*i.e.*, porphyrins and protoporphyrins).

Enclosed please find a copy of the final report for this study.

If you have any questions concerning this submission, please contact me at (703) 788-6570, kthomas@sehsc.com, or at the address provided herein.

Sincerely,

Karluss V. Thomas

Karluss Thomas
Executive Director

2009-SIEC-5510

**DOW CORNING CORPORATION**
HEALTH & ENVIRONMENTAL SCIENCES
TECHNICAL REPORT

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| | |
|---|---|
| **Study Title:** | Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test For Dimethylsilanediol (DMSD), ZMAT 4065555, in Sprague-Dawley Rats via Oral Gavage |
| **Study Number:** | 10872-102 |
| **Test Article:** | Dimethylsilanediol (DMSD) |
| **Study Director:** | Jeanne Y. Domoradzki, Ph.D., D.A.B.T. |
| **Sponsor:** | Silicones Environmental, Health and Safety Council<br>2325 Dulles Corner Blvd., Suite 500<br>Herndon, VA 20171 |
| **Sponsor Representative:** | Betsy D. Carlton, Ph. D., D.A.B.T.<br>BlueStar Silicones |
| **Testing Facility:** | Dow Corning Corporation<br>Health and Environmental Sciences<br>2200 West Salzburg Road<br>Auburn, MI 48611 |
| **Study Completion Date:** | August 12, 2009 |

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# 1 ABSTRACT

The objective of this study was to evaluate the potential toxicity of dimethylsilanediol in a 28-day combined repeated dose toxicity study with the reproductive/developmental toxicity screening test in Sprague-Dawley rats by oral gavage administration based on OECD Test Guideline 422, (1996). The test substance was administered by oral gavage in corn oil for 28 (toxicity group females) or 29 (males) days to 10 rats/sex/group (exception, female 50 mg/kg group where N=9) at 0, 50, 250 or 500 mg/kg/day. A single group of males was used for both the toxicity and reproductive phases of the study. Reproductive group females were treated (10 rats/dose group) for 14 days prior to the mating period, during the mating period and through post-partum day 3.

Animals were observed twice daily on weekdays and once daily on weekends and holidays for mortality or morbidity. Clinical observations were performed daily immediately following exposure. Body weight measurements were performed weekly. All animals received a detailed physical examination once before the first dose (to allow for within-subject comparisons), and weekly thereafter. Additional body weights on reproductive females were obtained on gestational days (GD) 0, 7, 14, and 20, within 24 hours of parturition, and on post-partum day four. Individual food consumption was recorded at least weekly, except during the cohabitation period. Functional observational battery (FOB) and motor activity evaluations were performed on males and toxicity group females once prior to initiation of exposures and during the 4th week of exposure. Blood samples for hematology and serum chemistry evaluations were collected at the scheduled necropsy from males and toxicity group females. Complete necropsies were performed on the males and the toxicity group females and selected organs were weighed. Microscopic examination was performed on protocol-specified tissues on all males and toxicity group females from the control and 500 mg/kg/day dose groups. Target tissues examined from the 50 and 250 mg/kg/day groups included liver, lung, prostate gland and thyroid gland from male rats and liver and lung from toxicity group female rats.

Mating was initiated after the first two weeks of exposure by pairing reproductive group females with males of the same treatment group until positive evidence of mating was obtained. Reproductive and developmental parameters evaluated included evidence of mating, pregnancy, duration of gestation, mean litter size, mean live litter size, mean litter weight, and mean ratio of live births/litter size. Dams and pups were euthanized on post-partum day 4 and examined for external gross lesions. The number of corpora lutea, and the number of uterine implantation sites were determined for all reproductive group females.

Oral gavage administration of dimethylsilanediol to male and female Sprague-Dawley rats at concentrations of up to 500 mg/kg/day for 28 (toxicity group females) or 29 (males) consecutive days was generally well tolerated. For the males at 250 and 500 mg/kg/day significant soiling was observed (abdominal region and urogenital soiling). Soiling of the muzzle was a significant abnormal observation in the toxicity group females at 500 mg/kg/day. Both abdominal soiling and urogenital soiling were significant abnormal observations in the reproductive group females at 500 mg/kg/day.

There were no statistically significant differences across exposure groups in the mean body weights on any day for toxicity group females and reproductive group females. In the males, there was a significant difference across treatment groups in week 2; however, there was not a significant difference between control and any of the treatment groups for that week.
With respect to body weight gain, 500 mg/kg/day males had a significant decrease in body weight gain during week 4 and in total gain from day 1 to 29. For 500 mg/kg /day toxicity group females, there was significant decrease in body weight gain during week 3. There were no statistically significant differences in body weight gain for the reproductive group females in any of the treatment groups during any of the measured intervals.

There were no differences in the average daily food consumption between control and treatment groups for the reproductive group females or the males and toxicity group females for any of the measured time periods.

There were no significant differences of toxicological significance between the control and treatment groups in either sex for the FOB ranked tests. There were no significant differences between either males or toxicity group females and their respective controls for the FOB continuous test and motor activity. There were no treatment-related changes associated with dimethylsilanediol administration on rat neurobiological function as evaluated with FOB and motor activity parameters.

The significant changes that were noted in hematological parameters and prothrombin times for males and toxicity group females were within or slightly below historical control values. There was no dose response with any of the hematologic parameters; however, there was a dose-related increase in male prothrombin times and a dose-related decrease in toxicity group female prothrombin times. The significant changes that were noted in clinical chemistry parameters for males and toxicity group females were within or slightly below historical control values. There were dose-related decreases in male and toxicity group female alkaline phosphatase and total bilirubin values as well as a dose related decrease in male aspartate aminotransferease values. No toxicological significance is assigned at this time to any statistically identified differences in clinical pathology since the findings were within or slightly below historical control ranges for this laboratory and the findings did not correlate with a pathological outcome.

The increased liver weights in males and toxicity group females at 250 and 500 mg/kg/day correlated with the histopathologic finding of centrilobular hypertrophy. There were no other treatment-related differences in organ weights (absolute and relative) for males and toxicity group females.

A standard set of protocol-defined tissues was examined for control and high-dose groups. Suspected target tissues were examined for 50 and 250 mg/kg/day groups. There were three primary effects of the test article observed in the liver, including centrilobular hypertrophy in both sexes, periportal hepatocellular vacuolation (microvesicular lipidosis, females only), and protoporphyrinosis (males only) which were accompanied by chronic inflammation and bile duct hyperplasia. Centrilobular hypertrophy is considered an adaptive change. Hepatic lipidosis, unless severe, is generally considered non-adverse. Hepatic protoporphyrinosis is considered an

adverse effect. Follicular cell hypertrophy was observed in the thyroid gland of 250 and 500 mg/kg/day male rats. This may reflect an adaptive secondary effect and adverse in the rat, but the mechanism is generally not applicable to species (such as humans) with significant levels of thyroid binding globulin (Capen, *et al.*, 2002). Lung (males and toxicity group females) and prostate gland were considered possible target tissues; however, further examination and inclusion of animals from the 50 and 250 mg/kg/day groups did not support this interpretation.

There were no treatment-related effects apparent for any of the reproductive endpoints: gestation length, litter size, litter weight, ratio live births/litter size, litter sex ratio, number of implantation sites, number of corpora lutea, post-implantation loss, post-natal loss, mating and fertility indices.

Based on liver results (protoporphyrinosis in males and vacuolation in toxicity group females) observed in this study, the systemic toxicity NOAEL (No-Observed-Adverse-Effect-Level) for dimethylsilanediol in rats via oral administration in corn oil is considered to be 250 mg/kg/day for male rats and toxicity group female rats. In the absence of adverse effects on reproductive or developmental parameters in this study, a NOAEL of 500 mg/kg/day is assigned for reproductive and developmental toxicity.

## 2 GLP COMPLIANCE STATEMENT

The study was conducted in compliance with the US EPA (TSCA) Good Laboratory Practice Standards 40 CFR Part 792.

GLP exception: Test article was not retained since storage stability has only been demonstrated for 66 days.

Protocol deviations are listed in Table 33. None were considered to impact results, interpretation or study validity.

Betsy D. Carlton, Ph.D., D.A.B.T.
Sponsor Representative
Bluestar Silicones

Date: 4 August 2009

Paul A. Jean, Ph.D.
Team Leader, Toxicology
Health and Environmental Sciences

Date: 12 Aug 09

Jeanne Y. Domoradzki, Ph.D., D.A.B.T.
Study Director
Health and Environmental Sciences

Date: August 12, 2009

# 3 QUALITY ASSURANCE STATEMENT

Title: Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test For Dimethylsilanediol (DMSD), ZMAT 4065555, in Sprague-Dawley Rats via Oral Gavage

Study Number: 10872-102

This study has been audited by the Dow Corning Corporation Health and Environmental Sciences Quality Assurance Unit according to approved Standard Operating Procedures to assure that the raw data are accurately reflected within this final report. The following are the inspection dates and the dates inspection findings were reported.

| Dates of Inspection | Phase Inspected | Findings Reported to Study Director | Findings Reported to Management |
|---|---|---|---|
| 21-22 May 2008 | Draft Protocol | 22 May 2008 | 06 June 2008 |
| 14 July 2008 | Dosing | 15 July 2008 | 17 July 2008 |
| 22 July 2008 | Serum Chemistry | 22 July 2008 | 23 July 2008 |
| 28 Oct 2008 | Facility Records | 28 Oct 2008 | 30 Oct 2008 |
| 25-26 Mar 2009 | Raw Data Review for Appendices A, B & C and Tables 1, 2, 3 and Associated Report Text | 26 Mar 2009 | 20 Apr 2009 |
| 25, 26, 27, 30 Mar 2009 | Draft Final Report and Raw Data Appendices D-I and Tables 4-9 | 31 Mar 2009 | 09 May 2009 |
| 01, 02 Apr 2009 | Draft Final Report and Raw Data Appendices J-L | 03 Apr 2009 | 09 May 2009 |
| 23 Mar-02 Apr 2009 | Contributing Scientist Report and Associated Raw Data for Appendix U | 02 Apr 2009 | 21 May 2009 |
| 3, 6, 7, 8, 9 Apr 2009 | Raw Data Review for Appendix N | 09 April 2009 | 28 Apr 2009 |
| 09, 10, 14-16 Apr 2009 | Contributing Scientist Report and Associated Raw Data for Appendix O | 16 Apr 2009 | 07 May 2009 |

| | | | |
|---|---|---|---|
| 13-20 Apr 2009 | Contributing Scientist Report and Associated Raw Data for Appendix M | 20 Apr 2009 | 08 May 2009 |
| 21-23 Apr 2009 | Contributing Scientist Report and Associated Raw Data for Appendix S | 23 Apr 2009 | 21 May 2009 |
| 22, 23 Apr 2009 | Draft Final Report and Raw Data for Appendices P and Q, Tables 27 and 28 | 23 Apr 2009 | 29 Apr 2009 |
| 23 Apr 2009 | Raw Data Review for Appendices R and Tables 31 and 32 | 23 Apr 2009 | 21 May 2009 |
| 01-24 Apr 2009 | Draft Final Report and Associated Raw Data | 24 Apr 2009 | 22 May 2009 |
| 13 May 2009 | Wet Specimen Verification | 13 May 2009 | 18 May 2009 |
| 06 July 2009 | Contributing Scientist Report and Associated Raw Data for Additional Statistical Work | 06 July 2009 | 20 July 2009 |

Linda Stilgenbauer, B.S.
Quality Assurance Auditor
Dow Corning Corporation
Health & Environmental Sciences

29 July 2009
Date

## 4 APPROVAL SIGNATURES

This report consists of 397 total pages, including Tables 1-33 and Appendices A – U. The undersigned have read and approved this report:

Betsy D. Carlton, Ph.D., D.A.B.T.
Sponsor Representative
Bluestar Silicones

4 August 2009
Date

Paul A. Jean, Ph.D.
Team Leader, Toxicology
Health and Environmental Sciences

12 Aug 09
Date

Jeanne Y. Domoradzki, Ph.D., D.A.B.T.
Study Director
Health and Environmental Sciences

August 12, 2009
Date

# 5 STUDY INFORMATION

| | |
|---|---|
| **Study Initiation Date:** | June 10, 2008 |
| **Experimental Start Date:** | June 15, 2008<br>(last animal dosed on August 9, 2008) |
| **Experimental Termination Date:** | February 25, 2009 |
| **Study Completion Date:** | August 12, 2009 |
| **HES Group Manager:** | Paul A. Jean, Ph.D.<br>Team Leader, Toxicology<br>Health and Environmental Sciences |
| **Study Coordinator:** | Linda S. Meeker, B.S., M.L.T., H.L.T. (A.S.C.P.) |
| **Contributing Scientists:** | Teresa Cortner, B.G.S.<br>Functional Observational Battery/Motor Activity |
| | James W. Crissman, D.V.M., Ph.D., D.A.C.V.P.<br>Pathology<br>Crissman Toxicologic Pathology, LLC<br>2887 Oakhaven Court<br>Midland, MI 48642-7869 |
| | Cynthia Van Landingham<br>Statistics<br>ENVIRON International Corporation<br>1900 North 18th Street<br>Suite 804<br>Monroe, LA 71201 |
| | Debra H. Stutts, B.S.<br>Analytical Chemistry |
| **Key Personnel:** | Jane M. Regan, MLT/HT (ASCP)<br>Clinical Pathology |
| **Lead Technician:** | Becki Uhlenhake |
| **Attending Veterinarian:** | Louis Llames, D.V.M., Ph.D. |
| **Manager, Analytical Chemistry** | Roy A. Campbell, B.S. |

## 6 STUDY PURPOSE

The objective of this study was to evaluate the potential toxic effects of dimethylsilanediol (DMSD) (supplied as Dow Corning™XX-1240 Dev Sample, ZMAT 4065555) following single daily oral gavage administration in corn oil to male and female Sprague-Dawley rats following 28 or 20 days of treatment or from before mating, through mating, and gestation and through post-natal day 3. Information on male and female reproductive performance including gonadal function, mating behavior, conception and parturition were evaluated.

## 7 GUIDELINES

The study design was based on and meets or exceeds the requirements of the following guidelines: OECD Test Guideline Number 422, (1996) and United States Environmental Protection Agency (USEPA) Health Effects Test Guideline OPPTS 870.3650 (2000).

## 8 TEST ARTICLE / SUBSTANCE / ITEM

The Study Director reviewed results of test substance characterization and that review was documented in the study file. The test substance characterization report is included in Appendix T.

| | |
|---|---|
| **Identification:** | Dimethylsilanediol (DMSD) (supplied as Dow Corning™XX-1240 Dev Sample, ZMAT 4065555) |
| **Reference Number:** | 21436-84 |
| **Expiration Date:** | August 15, 2008 |
| **Source:** | Dow Corning Corporation<br>Auburn, MI 48611 |
| **CAS Number:** | 1066-42-8 |
| **Physical Description:** | White solid |
| **Chemical Stability:** | Stable if stored at -20 to -80 °C over desiccant |
| **Purity:** | 97.8±0.01% |
| **Solubility:** | Soluble in water, ethanol |
| **Storage Conditions:** | Store at -20 to -80 °C over desiccant |
| **Chemical Characterization:** | HES Study Number: 10871-102 |

| | |
|---|---|
| **Archive:** | A reserve sample was not retained. Stability of test article at -65°C with a desiccant has not been shown for greater than 66 days. |

## 9 CARRIER

| | |
|---|---|
| **Identification:** | Corn Oil |
| **Lot Number:** | 117K0127 |
| **Expiration Date:** | May 28, 2009 (based on one year from date of receipt) |
| **Manufacturer:** | Sigma-Aldrich<br>3050 Spruce Street<br>Saint Louis, MO 63103 |
| **Physical Description:** | Deep yellow clear liquid, refer to MSDS |
| **Stability:** | Stable, refer to MSDS |
| **Purity:** | Used as provided by the manufacturer |
| **Storage Conditions:** | Stored in sealed container |

## 10 TEST SYSTEM

| | |
|---|---|
| **Species:** | Albino Rat |
| **Strain:** | Crl: CD® (SD) IGS BR VAF/Plus® |
| **Source:** | Charles River Laboratories, Inc.<br>401 S New Hope Rd<br>Raleigh, NC 27610 |
| **Age:** | 9 weeks minimum at dosing |
| **Body weight:** | Females: 167.0 to 198.8 g at experimental start<br>Males: 231.5 to 255.7 g at experimental start |
| **Number of animals ordered:** | 90 nulliparous and nongravid females<br>45 males |
| **Sex and number used on study:** | 80 nulliparous and nongravid females<br>40 males |
| **Number of groups:** | 4 |
| **Identification method:** | IMI-100 Transponders (BioMedic Data Systems, Inc. Seaford, DE) |

## 11 JUSTIFICATION FOR SELECTION OF TEST SYSTEM

The rat is recognized as appropriate for toxicity studies and is recommended in the OECD and OPPTS test guidelines. Sprague-Dawley rats (Crl: CD® (SD) IGS BR VAF/Plus®) have previously been used in repeated-dose toxicology studies of various silicones and are considered an appropriate strain for use in reproductive hazard assessment studies.

## 12 METHOD OF RANDOMIZATION

Extra animals were ordered and acclimated for randomization. After release from quarantine/acclimation, rats were assigned to test groups based on a weight stratified randomization method in Provantis™. Extra animals were placed in group 5 in the event that an animal needed to be replaced before the start of dosing. At randomization the sex-specific weight variation of animals in each group did not exceed ± 20% of the mean weight for that group. Disposition of all animals not utilized in the study is maintained on file at the Testing Facility.

## 13 HOUSING AND MAINTENANCE

### Animal Receipt and Quarantine/Acclimation

Animal resource personnel inspected each animal upon receipt and at least once daily during the quarantine period. Animals were quarantined/acclimated for five days. The attending veterinarian examined all animals before release from quarantine/acclimation. Animals judged to be in good health and suitable as test animals were released for study use.

### Animal Housing

Animals were individually housed in suspended wire-mesh cages elevated above fecal pans containing Bed-O'Cobs® litter, during quarantine/acclimation period and throughout the course of the study except during mating, gestation and lactation periods.

During cohabitation (mating), the reproductive group females were paired 1 to 1 with a male from the same treatment group. The animals were paired in the home cage of the male. After demonstrating positive evidence of mating the reproductive group female was individually caged. Pregnant females were moved into shoebox type cages containing Bed-O' Cobs® Combination bedding on day 0 of gestation and remained there throughout the remainder of the study. During the lactation period, dams were housed together with their litters. The Study Director reviewed the analysis of the Bed-O' Cobs® Combination bedding and found it free of contaminants that would have an impact on the outcome of the study.

The cages, bedding/fecal pans were routinely cleaned, consistent with good husbandry practices.

### Environmental Enrichment

Animals were given Nylabones® and Cozee Pads™ for environmental enrichment while in standard housing and Nylabones® only while in shoebox type caging. Environmental enrichment devices were removed from the toxicology animals the afternoon/evening prior to necropsy.

**Environmental Conditions**

Animals were housed in an environmentally controlled animal room (12-hour fluorescent-light/dark cycle, 20.19-23.24 °C, 50-67% humidity, 13.3 air changes per hour) throughout the study. Temperature and humidity were monitored continuously, recorded every 15 minutes using a HOBO Data Logger (Onset Computer, Bourne, MA; software: BoxCar Pro 4.3.1.1), and manually recorded twice daily on weekdays and at least once per day during weekends and holidays. The Study Director reviewed the last verification of air changes.

**Basal Diet**

Lab Diet 5002, Certified Rodent Diet (PMI Nutrition International), was provided *ad libitum* during the quarantine/acclimation period and throughout the study. Manufacturer's periodic analyses of the certified feed for the presence of heavy metals and pesticides maintained on file at the testing facility was reviewed by the Study Director to ensure that none were present in concentrations that may affect the outcome of the study.

Exceptions: Food was not provided during functional observation battery or motor activity assessment periods. Additionally, food was removed the day prior to necropsy of the toxicology group animals.

**Drinking Water**

Municipal water, further purified by reverse osmosis was available *ad libitum* via automatic watering system. Water is monitored routinely and also analyzed on a semi-annual basis. To ensure that no contaminants were present at a concentration expected to interfere with the integrity of the study, the Study Director reviewed the most recent analysis results maintained on file at the testing facility.

Exceptions: Water was not provided during functional observation battery or motor activity assessment periods.

## 14 ANIMAL WELFARE ACT COMPLIANCE

This study complied with all applicable sections of the final rules of the Animal Welfare Act regulations (9 CFR, Part 1, 2, and 3) and was approved by the Institutional Laboratory Animal Care and Use Committee (LACUC).

## 15 EXPERIMENTAL DESIGN

### 15.1 Data Acquisition System

Test system observations, body weights, food consumption, FOB, and morphologic pathology data, at a minimum, were collected using Provantis™v6.5 or v8.2 (Instem LSS, Conshohocken, PA). There were occasions, however, when manual collection of data was necessary. Excel 2003 was also used to create data tables.

## 15.2 Timeline of Study Events

| Endpoints | Toxicity Group Females | Males | Reproductive Group Females |
|---|---|---|---|
| Acclimation | 5 days (minimum) | 5 days (minimum) | 5 days (minimum) |
| Baseline FOB/ Motor Activity | 2-8 days prior to dosing | 2-8 days prior to dosing | _____ |
| Detailed Physical Examinations | Prior to dosing and weekly throughout the study | Prior to dosing and weekly throughout the study | Prior to dosing and weekly throughout the study |
| Dosing begins | Study Day 1 | Study Day 1 | Study Day 1 |
| Clinical Observations | Daily except when on day of detailed physical exam | Daily except when on day of detailed physical exam | Daily except when on day of detailed physical exam |
| Adult Body Weight | Randomization<br>Study Day 1<br>Weekly<br>Termination | Randomization<br>Study Day 1<br>Weekly<br>Termination | Randomization<br>Study Day 1<br>Weekly<br>GD** 0, 7, 14, and 20 within 24 hours after parturition<br>Day 4 post-partum |
| Food Consumption | Days 1, 8, 15, 22 and day prior to necropsy | Days 1, 8 and 15 | Day 1, 8 and 15<br>GD 0, 7, 14 and 20<br>Day 0 and 4 post-partum |
| Hematology/Clinical Chemistry | Termination | Termination | _____ |
| Mating (animals paired) | _____ | Study Day 15 up to Study Day 28 | Study Day 15 up to Study Day 28 |
| Treated FOB/Motor Activity | Week 4 | Week 4 | _____ |
| Gestation | _____ | _____ | Approximately 21 days |
| Parturition | _____ | _____ | Normally on day 21 or 22 post - coitum |
| Lactation | _____ | _____ | Until day 4 post - partum |
| Dosing ends | One day prior to the actual day of necropsy | One day prior to the actual day of necropsy | Day 3 post - partum |
| Termination | After a minimum of 28 treatment days on study | After a minimum of 28 treatment days on study | Day 4 post – partum* |

* Animals that delivered litters only. **GD = gestational day.

## 15.3 Route and Rationale of Test Substance Administration

**Route:**

Test article was administered by oral gavage in corn oil vehicle.

**Rationale:**

Oral gavage administration is an accepted method of administration of the test article and is recommended by the OECD and OPPTS Test Guidelines.

Based upon the physical and chemical properties of the test article, corn oil was considered to be the most appropriate vehicle for oral administration.

**Administration of doses:**

Vehicle/carrier only and test article suspensions were administered daily by oral gavage with a 15 gauge, 100 mm plastic oral feeding tube and syringe at a volume of 5 mL/kg body weight. Volume was adjusted based upon the most recent individual body weights.

## 15.4 Dosing Solution Preparation and Analysis

*Preparation*:

Frequency of dose solution preparation was determined to be every 7 days based on previous stability data of the test article in corn oil (Jean and Meeker 2007). The stability of DMSD in corn oil for this study was determined to be 11 days and the results of this analysis are included in the study file. The frequency of dose suspension preparation was based on the 11 day stability data. DMSD was ground to a fine powder using a mortar and pestle. Dosing solutions were prepared by weighing the appropriate amount of the test article into a tarred container and adding the appropriate amount of corn oil to yield the desired dose level. Calculations and preparation methods are documented in the raw data.

*Analysis:*

A GC/FID method was used by Dow Corning HES to verify concentration, stability, and homogeneity of the test article in carrier. All details of the GC method are documented in the study records.

Concentration verification was conducted for the initial dose preparations for each lot/reference number of test article. There was one lot of material used. Homogeneity determinations were performed on the high and low dose suspensions prepared from the first lot of test article used. Triplicate samples were taken from three different locations to determine homogeneity of the high and low dose solutions.

*Storage Conditions:*

The dosing suspensions were stored at 5 ± 4°C in sealed glass vials that were placed into sealed plastic bags containing desiccant or a desiccator with desiccant, and allowed to warm to room

temperature prior to dosing. There were two occasions where the storage conditions were out of temperature range and these are noted in Table 33.

### 15.5 Test Groups and Dose Levels

Organization of test groups and test article dose levels are presented in the table below. A total of 30 animals were assigned to each dose group. Ten female animals per dose group were placed on study for the purpose of toxicological evaluation only (toxicity group). Ten female animals per dose group were placed on study for the purpose of evaluating reproductive endpoints only (reproductive group). Ten male rats per dose group were place on study for the purpose of evaluating both reproductive and toxicological endpoints. Animal 5504 was moved from the female toxicity group, 50 mg/kg/day, to the female reproductive group, 50 mg/kg/day during week 2 of the study.

The dose levels were selected based on results from a previous range finding study (Jean and Meeker 2007) and to provide dose-response data for the test article.

**Organization of Test Groups and Dose Levels**

| Group | Number of Animals | | Dose Level (mg/kg/day) | Animal ID Numbers | Animal ID Numbers |
|---|---|---|---|---|---|
| | Toxicity Group | Reproductive Group | | Toxicity Group | Reproductive Group |
| 1m | 10 males | ** | 0 | 5484 – 5493 | |
| 1f | 10 females | 10 females | | 5474 – 5483 | 5494 – 5503 |
| 2m | 10 males | ** | 50 | 5514 - 5523 | 5504 and 5524 - 5529, 5531 - 5533 |
| 2f | 10 females | 10 females | | 5505 - 5513 | |
| 3m | 10 males | ** | 250 | 5544 - 5553 | |
| 3f | 10 females | 10 females | | 5534 - 5543 | 5554 - 5563 |
| 4m | 10 males | ** | 500 | 5574 - 5583 | |
| 4f | 10 females | 10 females | | 5564 - 5573 | 5584 - 5593 |

Animal 5530 was euthanized on Day 3 of study due to a gavage error.
Animal 5504, originally in group 2 toxicity group females was then assigned to the reproductive female group 2 during week 2.
** - Ten male rats per dose group were place on study for the purpose of evaluating both reproductive and toxicological endpoints.

### 15.6 Treatment Regimen

Carrier only and test substance in carrier were administered once daily by oral gavage, seven days per week, at approximately the same time each day. Treatment of both sexes began two weeks prior to initiating mating and continued through the mating period. Male and toxicity group females were treated for 28 and 29 days, respectively, and euthanized the day after the last treatment. The males were used to assess both toxicity and reproductive effects. Reproductive group females were treated through post-partum day 3 or until euthanized in extremis.

## 15.7 Mating Procedure

A 1:1 mating ratio was used. On study Day 15, the animals were paired by placing the lowest identification number (ID) numbered reproductive group female of each group with the lowest ID numbered male of that group, then the next lowest ID numbered reproductive group female with the next lowest numbered male, etc., until all animals were paired. The reproductive group females were housed continuously with the same male until evidence of mating occurred or two weeks had elapsed. Proven males from the same dose level did not need to be used to maintain a 1:1 mating ratio since male mortality did not occur in this study. Reproductive group females were evaluated daily for evidence of copulation, by confirming the presence of either a vaginal copulatory plug or sperm in the vaginal smear. Day 0 of gestation was defined as the day evidence of copulation was observed, at which time the reproductive group female was returned to her home cage.

## 15.8 Method of Disposition

*Scheduled*

All males and toxicity group females were euthanized by exsanguination. While under Isoflurane® anesthesia blood was collected from the caudal vena cava followed by the cutting of major abdominal vessels.

The reproductive group females were euthanized by $CO_2$ inhalation on postpartum day four. Nongravid females demonstrating no evidence of copulation were euthanized 24-26 days after the last day of the mating period. Reproductive group females with evidence of copulation that did not deliver were euthanized on gestation day 24-27. No reproductive group females displayed signs of distress during pregnancy or delivery that would warrant euthanasia prior to scheduled termination.

Day four pups were euthanized by intraperitoneal injection with either Euthasol or Socumb.

*Unscheduled*

Measures were taken to minimize discomfort or pain for all animals. If the health of an animal was deemed to be unacceptable for continuation on study, the animal was euthanized by $CO_2$ inhalation for adults, isoflurane/decapitation for pups, or immediate decapitation for cannibalized pups. The decision to euthanize an animal, 5530, was made on day 3 following a gavage error. Adult animals were subjected to a gross necropsy. A complete set of tissues (see Morphologic Pathology) were collected from males and toxicity group females. Collection of tissues from adult reproductive group females was at the discretion of the Study Director and/or Study Pathologist and tissues were not taken.

## 15.9 Test System Observations

*Mortality/Morbidity/Moribundity*

All animals were observed at least twice daily (once daily on weekends and holidays) in their cages for mortality, morbidity, and moribundity by study personnel throughout the completion of the in-life phase of the study. No animals were found dead. Pups found dead were examined for

external gross abnormalities only. The Study Director (or designee) and Attending Veterinarian (or designees) were notified when animals were found sick, moribund, or dead.

*Clinical Observations*

General clinical observations were made at least once a day, beginning on the first day of treatment, at approximately the same time(s) each day. During the week prior to necropsy when FOB and MA are conducted, the animals are dosed at a later time and clinical observations were conducted after dosing. The health condition of the animals was recorded. Findings noted at the clinical examination were recorded for individual animals. Daily observations were also performed on all animals on the day of, but prior to, their scheduled necropsy.

Clinical observations were not performed on the day of the detailed clinical observations or detailed physical exams.

*Detailed Physical Examinations or Detailed Clinical Observations*

All animals received a detailed physical examination once before the first dose (to allow for within-subject comparisons), and weekly thereafter. The observations were made outside the home cage in a standard arena at approximately the same time each day. Observations were detailed and carefully recorded. Signs noted included, but were not limited to, changes in skin, fur, eyes, mucous membranes, occurrence of secretions and excretions and autonomic activity (e.g., lacrimation, piloerection, pupil size, unusual respiratory pattern). Changes in gait, posture and response to handling as well as the presence of clonic or tonic movements, stereotypies (e.g., excessive grooming, repetitive circling), difficult or prolonged parturition or bizarre behavior (e.g., self mutilation, walking backwards) were recorded. The presence or absence of findings was recorded for individual animals.

*Female Reproductive Group Observations*

The duration of gestation was calculated from day 0 gestation for each reproductive group female. From gestation day 20 after evidence of mating, pregnant animals were checked at least three times daily (twice daily on weekends and holidays) for evidence of parturition. If difficulties were observed, progress of the parturition process was monitored.

## 15.10 Parameters Measured

*Individual Body Weights*

Individual body weights were determined beginning with randomization into test groups, on the first day of dosing, at least weekly thereafter, and on the day of euthanasia since no animals were found dead. During gestation, the reproductive group females were weighed (at a minimum) on gestation days 0, 7, 14 and 20, within 24 hours after parturition, and day 4 post-partum. Litter weights were taken within 24 hours of parturition and on day 4 post-partum.

*Individual Food Consumption*

Individual animal food consumption was recorded at least weekly for the periods listed below.

**Male rats**:

Two week pre-mating period only.

Feeder weights were taken on days 1, 8, and 15.

Deviation: Due to an unanticipated event, the total grams of food for week 1 were estimated for most animals in the control group from daily values calculated from day 5 to day 8. This

estimation was done by adding in 4 average daily values based on the average daily value calculated from the difference between days 5 and 8.

**Female rats:**
*Toxicity group:*
Feeder weights were taken on day 1, 8, 15, 22 and the day prior to necropsy.
Deviation: Due to an unanticipated event, the total grams of food for week 1 were estimated in the control group from daily values calculated from day 5 to day 8. This estimation was done by adding in 4 average daily values based on the average daily value calculated from the difference between days 5 and 8.

*Reproductive group:*
Feeder weights were taken on days 1, 8, 15, and on gestation days 0, 7, 14, 20, and on days 0 and 4 post-partum.

*Functional Observational Battery*
Functional Observational Battery (FOB) and Motor Activity evaluations were performed on all adult males and all Toxicity Group females prior to dosing (baseline evaluations) and during the fourth week of dosing. Since animal 5504 was moved into the female reproductive group during the second week of dosing, the female toxicity group at the 50 mg/kg/day dose level had an N of 9 for FOB and Motor Activity evaluations. Testing performed during the fourth week of dosing took place prior to the daily dosing. FOB and Motor Activity examinations were performed on all animals since signs of toxicity were not observed to an extent that would significantly interfere with the evaluation.

Baseline evaluations were also performed on the "extra" or "reserve" animals (Group 5) in the event that a replacement was needed for an animal already on study. An "extra" animal, 5600, took the place of animal 5540 (ID changed from 5600 to 5540) on the first day of dosing. Data collected on animals which were not subsequently used on study are not included in the final report.

Animals were observed for the following as described below:

***Cage Side Observations:***

abnormal muscle movements (e.g., tremors, convulsions), abnormal behavior (e.g., circling, stereotypy), posture and resistance to removal

***Hand-held Observations:***

palpebral closure, lacrimation, pupil size, pupil reactivity, salivation, muscle tone, extensor thrust response, and reactivity to handling

***Open Field Observations:***

a one minute evaluation of level of activity (ambulatory and rearing), responsiveness to sharp noise, touch, and tail pinch, gait evaluation, quantity of urine and fecal pellets voided

***Categorical Observations:***

(can be made any time during the FOB) behavior, skin/fur/mucous membrane, respiration, muscle, eyes, urine or feces, soiling, posture and other abnormalities

***Measurements/Counts:***

rectal temperature, hind-limb/forelimb grip strength, landing foot splay

***Motor Activity:***

Locomotor activity was determined using a Cage Rack Activity System (CRAS) purchased from San Diego Instruments (San Diego, CA) and PAS v.2.03 software.

*Reproductive Parameters*

Each litter was examined as soon as possible after delivery to determine the number and sex of the pups, the number of pups alive, number of dead pups, runts, and the presence of any gross abnormalities. Pups were counted and sexed and litter weights were taken within 24 hours of parturition and on day 4 post-partum. The day parturition was observed as complete was considered day 0 post-partum. Any abnormal behavior of the offspring was recorded.

*Clinical Pathology*

Clinical Pathology assessments were made on all surviving adult males and toxicity group females from which adequate samples were collected. Food was removed on the evening prior to scheduled necropsy.

Blood samples were collected for hematological and clinical chemistry evaluations from all males and all toxicity group females on the day of scheduled euthanasia as a terminal procedure. While under Isoflurane® anesthesia a syringe and needle were used to collect blood samples from the abdominal vena cava and distributed to three sample collection tubes containing either sodium citrate, EDTA, or no anticoagulant.

If blood sample volume was inadequate to distribute into three collection tubes, the sample was first distributed into the EDTA collection tube and then the collection tube without anticoagulant, if volume permitted. If at any time during distribution a blood clot was observed, all remaining sample was placed into the collection tube without anticoagulant.

***Hematology***

Blood samples for the following hematology tests were collected into test tubes containing EDTA:

| | |
|---|---|
| Erythrocyte count (RBC) | Hemoglobin (Hgb) |
| Erythrocyte Indices (MCV, MCH, MCHC) | Hematocrit (Hct) |
| Leukocyte counts (WBC, total and differential) | Platelet count (PLT) |

Hematology samples were analyzed within 48 hours of collection. If analysis was not performed within eight hours the hematology samples were stored at 2-8°C. Clotted or

grossly hemolyzed samples were not analyzed. Methods of analysis were documented in the raw data and are presented in this study report.

***Coagulation***

Blood samples for coagulation assessment (prothrombin time) were placed into test tubes containing sodium citrate, centrifuged within two hours of collection and the plasma separated for testing. Clotted or grossly hemolyzed samples were not be analyzed for coagulation. Plasma samples were analyzed by nephelometry using the ACL 100 (Instrumentation Laboratory Company, Lexington, MA).

***Serum Chemistry***

The following serum chemistries were determined:

| | |
|---|---|
| Alanine aminotransferase | Glucose |
| Albumin | Phosphorus |
| Alkaline phosphatase | Potassium |
| Aspartate aminotransferase | Sodium |
| Calcium | Total bilirubin |
| Cholesterol | Total protein |
| Chloride | Urea nitrogen |
| Creatinine | |

Blood samples were placed into test tubes not containing anticoagulant, allowed to clot and centrifuged within two hours of collection and the serum separated for testing. Serum samples were analyzed on the Cobas Intergra 400 plus® (Roche Diagnostics, Indianapolis, IN).

*Morphologic Pathology*

***Macroscopic Examination***

*Males and Toxicity Group Females:* All males and toxicity group females (N=9 in 50 mg/kg/day dose level) were subjected to a complete gross necropsy that included: examination of the external surface and all orifices of the body, the cranial, thoracic and abdominal cavities and their contents.

*Reproductive Group Females:* For reproductive group females, the number of corpora lutea and the number of implantation sites were recorded. Dead pups and pups euthanized on day 4 post-partum were examined for external gross abnormalities only. Pup tissues were not scheduled for collection and the carcasses were discarded. For any reproductive group female with positive evidence of mating that failed to produce a litter, the uterus was stained to enable counting of possible reabsorbed implant sites. There was one reproductive group female each in the following dose groups; 0 (5501), 50 (5533) and 250 (5561) mg/kg/day, where there was positive evidence of copulation, however the

animals were not pregnant. The uteris were stained with an equal mixture of 20% Potassium Ferricyanide and 1% Hydrochloric Acid. A uterus from a control group dam was stained and used as a positive control. No implantation sites were found in the non-pregnant animals; 5501, 5533 and 5561.

***Microscopic Examination***

Selected tissues and organs (identified below) required for histopathological examination from all males and toxicity group females were taken and preserved in fixative. Selected organs were also weighed.

| Organ Weights* | Organs Collected** |
|---|---|
| | Macroscopic lesions |
| X | Adrenals |
| X | Brain (including cerebrum, cerebellum and pons) |
| | Cecum |
| | Colon |
| | Duodenum |
| X | Epididymides |
| X | Heart |
| | Ileum |
| | Jejunum |
| X | Kidneys |
| X | Liver |
| | Lungs (preserved by inflation with fixative and then immersion) |
| | Lymph nodes (mediastinal and mesenteric) |
| X | Ovaries |
| X | Prostate |
| | Sciatic nerve |
| X | Seminal vesicles |
| | Spinal cord (cervical, thoracic and lumbar) |
| X | Spleen |
| | Sternum with bone marrow |
| | Stomach |
| X | Testes |
| X | Thymus |
| | Thyroid |
| | Trachea |
| | Urinary bladder |
| X | Uterus (horns and cervix) |

*Paired organs were weighed together.

**The testes and epididymides were preserved in Bouin's solution. All other tissues collected were placed in 10% neutral buffered formalin for preservation.

A histopathological examination was conducted on the collected tissues from the adult animals in the control and high dose groups (males and toxicity females). All gross lesions were examined. Histopathological examination was extended to target tissues (males: liver, lungs, thyroid gland, prostate gland and toxicity group females: liver and lungs) in the low- and mid-dose groups.

### 15.11 Sample Identification

Samples collected were identified by study number, test system or specimen number, identity/name of sample, date of collection and storage conditions.

## 16 DATA ANALYSIS

### 16.1 Parameters evaluated

Mean body weight values and body weight changes, mean food consumption values, mean hematology and clinical chemistry values, mean terminal organ weights and organ/bodyweight ratios, mean gestation length, mean litter size, mean live litter size, mean litter weight, mean ratio live births/litter size, litter sex ratio, mean number of implantation sites, mean number of corpora lutea, mean mating and fertility indices, and mean neurotoxicological parameters were evaluated as appropriate.

### 16.2 Statistical methods

Data analysis was carried out using Provantis™ v6.5 or v8.2 with SAS v9.1.3 or with SAS v9.1.3 (SAS Institute, 2006). Body weight, changes in body weight, organ weight, organ to body weight ratios, food consumption data, hematology data, clinical chemistry and prothrombin times were analyzed using a one-way Analysis of Variance (ANOVA) if the data satisfied the requirements of normality of the residuals and homogeneity of variance as determined using a statistical test for normality for homogeneity of variance (Gad and Chengelis, 1998). If the data do not satisfy the parametric requirements, a Kruskal-Wallis test was used (Kruskal and Wallis, 1952; Kruskal, 1952). If the ANOVA or Kruskal-Wallis test was significant ($p < 0.05$), pair-wise comparisons of the exposed groups to control were made using the Dunnett's test (Dunnett, 1955, 1964) or a Wilcoxon test, respectively.

For variables with multiple measurements across time (motor activity, body weight and food consumption), a repeated measurements ANOVA was performed to determine if a significant time by treatment group interaction exists. Repeated measurements ANOVAs were done using the time (baseline and post-treatment), interval, sex and treatment to look for interactions between the treatment, the time and sex to determine if analysis could be done with the sexes combined.

Reproductive parameters with the exception of litter size were analyzed using an ANCOVA (Analysis of Covariance) with litter size as the covariate. Litter size was analyzed using an ANOVA.

Measured continuous Functional Observational Battery (FOB) data were analyzed using a combination of ANCOVA with baseline evaluations used as the covariate and repeated measures ANOVA. Categorical FOB data was analyzed using the Jonckheere-Terpstra test (Jonkheere, 1954).

Categorical Functional Observational Battery (FOB) data were analyzed using the Jonckheere-Terpstra test. This test is used to detect a shift in the categorical observations.

Microscopic findings were also analyzed using a Cochran-Armitage trend test to indicate an increasing incidence trend with Fisher's Exact tests used to indicate increased incidence over the control.

Clinical signs data were analyzed using Mixed Modeling repeated measures. Mixed models represent the fixed effect of treatments and the random effect of variability from animal to animal and observation to observation (within animal). Mixed models are generalizations of standard linear models (e.g., analysis of variance) and the SAS procedure PROC MIXED can be used in instances where every animal was not examined at every time point without loss of observations as would occur when using PROC GLM to do a repeated measurement ANOVA. The repeated measures aspect of the analysis recognizes that the variability in the responses is the result of animal-to-animal variability and of variability among the individual observations within each animal over the course of the study. Using the SAS procedure PROC MIXED, the model was defined as

Response = exposuregrp,

where, exposuregrp indicates the class variable associated with each exposure level, with animal as the "subject" (where the "subject" is the unit for which there are repeated observations), and the response was a binomial variable indicating that the animal had or did not have a specific abnormal response at each time point for which examination data was available. Such a mixed model represents the mean responses as a function of the exposure group with variation (standard errors) that account for animal-to-animal and within-animal variability. As in an analysis of variance, the exposure groups were examined to determine if there was an overall "treatment effect" and, if there was, then pair-wise comparisons of the individual exposed groups to the control group were completed.

## 17 PROTOCOL DEVIATIONS

Protocol deviations are presented in Table 33. There were no deviations that adversely affected the quality or integrity of the study data.

## 18 RESULTS AND DISCUSSION

## 18.1 Mortality and Morbidity

All but one animal survived to their scheduled necropsy. Animal 5530 was euthanized on the third day of the study due to an oral gavage error.

## 18.2 Clinical Observations

The incidence of clinical observations are summarized in Tables 1-3. Individual clinical examination data are presented in Appendices A-C. Observations recorded during the weekly detailed physical examinations were not different from those recorded during the daily clinical examinations. Therefore, the findings were combined and are presented in total. For the males at 500 mg/kg/day, significant abnormal observations ($p<0.01$) were noted and included soiling in the abdominal region and urogenital soiling. Urogenital soiling was also significant ($p<0.05$) in males at 250 mg/kg/day. Soiling of the muzzle was a significant abnormal observation ($p<0.02$) in the toxicity group females at 500 mg/kg/day. Both abdominal soiling and urogenital soiling were significant abnormal observations ($p<0.01$) in the reproductive group females at 500 mg/kg/day.

## 18.3 Body Weight

Summaries of weekly mean body weights are shown in Tables 4-6. Mean body weight gain summaries are shown in Tables 7-9. Individual animal body weight data and body weight gain data are given in Appendices D-F and Appendices G-I, respectively.

There were no statistically significant differences across treatment groups in the mean body weights on any day for any of the three groups: males, toxicity group females, and reproductive group females. With respect to body weight gain, 500 mg/kg/day males had a statistically significant decrease in body weight gain ($p<0.05$) during week 4. The 500 mg/kg/day male group also had a statistically significant decrease ($p<0.02$) in total gain from day 1 to 29. For 500 mg/kg/day toxicity group females there was a statistically significant ($p<0.02$) in body weight gain during week 3. There were no statistically significant differences in body weight gain for the reproductive group females in any of the treatment groups: week 1 and 2 pre-mating, gestational weeks 1, 2, 3 and post-partum day 0 to post-partum day 4. Weight gain for the reproductive group females in the three treatment groups was not different from control for the interval from day 1 of study to post-partum day 4.

## 18.4 Food Consumption

Weekly mean food consumption data are presented in Tables 10-12. Individual animal food consumption values are given in Appendices J-L. There were no differences in the average daily food consumption across treatment groups for the reproductive group females or the toxicity group females for any of the measured time periods. In the male group there was a significant difference across treatment groups in week 2, however, there was not a significant difference between control and any of the treatment groups for that week.

## 18.5 Functional Observation Battery and Motor Activity

Functional Observation Battery (FOB) and Motor Activity data are presented in Tables 13-18 and individual animal values presented in a contributing scientist report, Appendix M. No statistically significant differences between the control and treatment groups in either sex at the

treated time point for all the FOB ranked tests, except for an increase in defecation (males) at 500 mg/kg/day at a significance of $p < 0.05$. There was no dose response associated with this effect, nor did it correlate with any change in the other neurobehavioral tests conducted on the same animals. There were no statistically significant differences between either males or toxicity group females and their respective controls for the FOB continuous test and motor activity. There were no treatment-related changes associated with dimethylsilanediol administration on rat neurobiological function as evaluated with FOB and motor activity parameters.

## 18.6 Clinical Pathology

**Hematology:**

Group mean summaries of hematology parameters are given in Tables 19-22 and Appendix N.

Compared to control, 500 mg/kg/day male rats (Table 19) had statistically significant decreases for hemoglobin ($p < 0.01$) and mean cell hemoglobin ($p < 0.01$) and hematocrit ($p < 0.05$). The group mean values for hemoglobin (13.49 g/dL) and hematocrit (39.63 %) were slightly below historical control ranges (13.6-16.1 g/dL and 40.0-45.9%, respectively). The mean cell hemoglobin value of 18.41 pg was within the historical control range (18.0-20.9 pg).

Statistically significant decreases at $p<0.01$ were observed between control and 500 mg/kg/day toxicity group females (Table 20) for hemoglobin (13.92 g/dL) and mean cell hemoglobin concentration (33.13. g/dL). These were both within historical control ranges of hemoglobin and mean cell hemoglobin concentration, 13.8-15.8 g/dL and 32.7-36.6 g/dL, respectively.

There were no significant differences noted in the other hematology values or hematology differential data across groups for either sex. No toxicological significance is assigned at this time to any statistically identified differences in hematology parameters since the findings were within or slightly below historical control ranges for this laboratory and the findings did not correlate with a pathological outcome.

**Prothrombin Times:**

Prothrombin times are summarized in Table 23 and Appendix N.

A statistically significant increase ($p<0.01$) in prothrombin times was noted in 250 and 500 mg/kg/day males, 14.81 and 15.86 seconds, respectively (Table 23). The 250 and 500 mg/kg/day toxicity group females had statistically significant decreases in prothrombin times; 13.20 and 13.09 seconds, respectively. These values were within historical control ranges for males and females of 11.6-19.5 and 10.7-17.5 seconds, respectively. Statistically significant prothrombin times were within historical control ranges; however, there was a dose-related increase or decrease. Changes in prothrombin times were considered treatment-related but of no toxicological significance.

**Clinical Chemistry:**

Clinical chemistry data summaries are presented in Tables 24 and 25 and individual animal data are presented in Appendix N.

Statistically significant differences were observed in the male rats (Table 24) for alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total bilirubin, BUN, sodium, albumin, and total protein. Alkaline phosphatase (250 mg/kg/day, 100.0 U/L; 500 mg/kg/day, 89.8 U/L) and total bilirubin (250 mg/kg/day, 0.086 mg/dL; 500 mg/kg/day, 0.084 mg/dL) were statistically decreased ($p < 0.01$) in male rats at 250 and 500 mg/kg/day. A significant increase ($p<0.01$) for alanine aminotransferase (27.1 U/L) was seen at 500 mg/kg/day. These parameters were within historical control ranges of this laboratory for male Sprague-Dawley rats: alkaline phosphatase (80-227 U/L), alanine aminotransferase (13.0-36.0 U/L), and total bilirubin (0.07-0.31 mg/dL. Aspartate aminotransferase (AST) had statistically significant decreases in males at 50, 250 and 500 mg/kg/day ($p < 0.05$, $p < 0.01$ and $p<0.01$, respectively). The mean values for AST were 70.8, 58.0 and 48.8 U/L, respectively with the value for 500 mg/kg/day below the historical control range (55-129 U/L). A significant decrease ($p < 0.05$) was seen for albumin at 250 mg/kg/day (3.57 g/dL) and a significant increase ($p < 0.05$) was observed for total protein at 500 mg/kg/day (5.94 g/dL). The BUN was statistically increased ($p < 0.01$) for 500 mg/kg/day males (14.4 mg/dL). These observations with albumin, total protein and BUN were within historical control values of 2.8-4.2 g/dL, 5.2-6.7 g/dL and 9-17 mg/dL, respectively. Sodium at 139.8 mmol/L was statistically decreased ($p< 0.01$) at 500 mg/kg/day; however, it was within the historical control range (139-146 mmol/L).

Statistical significant differences were observed in the toxicity group females (Table 25) for alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total bilirubin, and cholesterol. Alkaline phosphatase (250 mg/kg/day, 58.8 U/L; 500 mg/kg/day, 48.3 U/L) and bilirubin (250 mg/kg/day, 0.092 mg/dL; 500 mg/kg/day, 0.088 mg/dL) were statistically decreased ($p < 0.01$, ALP and $p < 0.05$, TBILI) in 250 and 500 mg/kg/day toxicity group females. A significant increase ($p<0.01$) for alanine aminotransferase (26.9 U/L) was seen at 500 mg/kg/day. Aspartate aminotransferase (76.0 U/L) was statistically increased, $p < 0.05$, at 50 mg/kg/day. The cholesterol value (85.7 mg/dL) was statistically increased at $p<0.01$ for 500 mg/kg/day toxicity group females. These parameters were within historical control ranges of this laboratory for female Sprague-Dawley rats: alkaline phosphatase (36-125 U/L), alanine aminotransferase (11.0-56.0 U/L), aspartate aminotransferase (49.0-119.0 U/L), total bilirubin (0.09-0.34 mg/dL), and cholesterol (31-99 mg/dL).

There were no significant differences noted in the other clinical chemistry values across groups for either sex. There were dose-related decreases in male and toxicity group female alkaline phosphatase and total bilirubin values as well as a dose related decrease in male aspartate aminotransferease values. No toxicological significance is assigned at this time to any statistically identified differences in clinical pathology since findings were within or slightly below historical control ranges for this laboratory and the findings did not correlate with a pathological outcome.

### 18.7 Organ Weights

Organ weight and organ to body weight ratios are summarized in Tables 27-28 and individual animal data are presented in Appendices P-Q.

There were statistically significant differences noted for the following organ weights in males; adrenal glands (24% decrease at 500 mg/kg/day at $p < 0.01$), liver (19% increase at 250 and 31% increase at 500 mg/kg/day at $p < 0.01$), testes (12% decrease at 500 mg/kg/day at $p < 0.01$), and thymus (31% decrease at 500 mg/kg/day at $p < 0.01$). There were statistically significant differences for the mean percentage of organ weights relative to body weights for adrenal glands (decrease at $p < 0.05$), liver (increase at 250 and 500 mg/kg/day at $p < 0.01$), and thymus (decrease at $p < 0.05$) for the males.

There were statistically significant differences noted liver weights in toxicity group females; liver (24% increase at 250 and 61% increase at 500 mg/kg/day at $p < 0.01$). There were statistically significant differences for the mean percentage of organ weights relative to body weights for liver (increase at 250 and 500 mg/kg/day at $p < 0.01$) for the toxicity group females.

The increased liver weights in males and toxicity group females correlated with the histopathologic finding of centrilobular hypertrophy. There were no other treatment-related differences in organ weights, absolute and relative (mean %) for males and toxicity group females.

## 18.8 Morphological Pathology

**Macroscopic Examination:**

Macroscopic pathology data are presented in Table 26 and a contributing scientist report in Appendix O.

In the liver, the finding of discoloration (+/- mottled) was observed more commonly in rats of both sexes administered ≥250 mg/kg/day. Liver enlargement was grossly more notable in toxicity group females administered 500 mg/kg/day. Lung discoloration was more common in male rats administered ≥250 mg/kg/day. Other findings generally occurred singly and were not considered to be attributable to test article administration.

**Microscopic Examination:**

The incidence and severity of microscopic findings are summarized in Tables 29-30 and individual animal data are presented in a contributing scientist report in Appendix O.

**Liver**

Males

There were two primary liver findings in male rats. In the liver of male rats, the incidence of centrilobular hypertrophy was significantly increased ($p < 0.01$) in 250 and 500 mg/kg/day groups (8/10 animals in each group) over control. The increased incidence of centrilobular hypertrophy identified correlates with the statistically significant increase in relative liver weight observed for these groups. This is a common effect of xenobiotic administration and is considered an adaptive change (Cattley and Popp, 2002).

Additionally, there was minimal to moderate brown pigment accumulation in and around bile ducts, with associated bile duct hyperplasia and chronic inflammation in 9/10 500 mg/kg/day males. The pigment was birefringent under polarized light, appearing bright red with Maltese cross patterns, characteristic of protophorphyrin (Greaves, 2000; DeMatteis *et al.*, 1987). The finding was split into three components and recorded as 1) protoporphyrinosis, 2) periportal chronic inflammation, and 3) bile duct hyperplasia associated with protoporphyrinosis. The severity of the inflammatory and bile duct hyperplasia components generally closely matched the pigment accumulation. The brown pigment was not observed in control animals, at lower dose levels, or in female rats. Periportal chronic inflammation (9/10 animals), hyperplasia in the bile ducts associated with protoporphyrinosis (8/10 animals), and protoporphyrinosis (9/10 animals) showed significant increase in incidence ($p<0.01$) over control only in the 500 mg/kg/day group. For these microscopic findings in the liver, there were no significant shifts in severity across treatment groups.

Toxicity Group Females

In the liver, the incidence of centrilobular hypertrophy was significantly increased ($p <0.01$) in the 250 and 500 mg/kg/day toxicity group females. The increased incidence of centrilobular hypertrophy identified correlates with the statistically significant increase in relative liver weight observed for these groups. This is a common effect of xenobiotic administration and is considered an adaptive change (Cattley and Popp, 2002).

Liver periportal vacuolation, was significantly ($p <0.02$) increased in incidence over the control group only for the 500 mg/kg/day toxicity group females. Comparison of the graded animals only showed a significant increase in severity grade across treatment groups for liver vacuolization in females. It is generally but not universally held that this finding in and of itself is not considered adverse unless severe (Cattley and Popp, 2002).

**Thyroid Gland**

Both the 250 and 500 mg/kg/day male toxicity groups (8/10 and 9/10 animals, respectively) had significantly increased incidence ($p <0.01$) of thyroid gland follicular hypertrophy than did the control group and the comparison of the graded animals showed a significant increase in severity grade across treatment groups. Hypertrophy of the thyroid follicular epithelium is a common secondary response to increased thyroid hormone catabolism due to up-regulation of hepatic microsomal enzymes in response to xenobiotic administration (Capen *et al.*, 2002). The rat is particularly sensitive to this effect due to the species' lack of a protective carrier protein, thyroid binding globulin.

**Prostate Gland**

The 500 mg/kg/day group had a statistically significant increase in incidence ($p <0.05$) in chronic inflammation of the prostate gland over that seen in the control group. Chronic inflammation of the prostate gland is a fairly common spontaneous finding (Bosland, *et al.*, 1998). This finding is not considered to be attributable to test article administration, particularly since the two most severe instances occurred in rats administered 0 and 50 mg/kg/day

**Lung**

In the lungs of males rats, there was an increasing trend in the observed incidence of pulmonary histiocytosis (aggregates of foamy macrophages. For histocytosis in the lungs there were no pair wise significant differences between any treated group and control. This is a very common spontaneous finding (Renne, *et al.,* 2003) and there was no clear increase in severity associated with dosage. This finding is not considered to be attributable to test article administration.

## 19 Reproductive Parameters

The mean values for reproductive parameters are presented in Tables 31 and 32 and individual animal data are given in Appendix R. Three reproductive group females, 5501 (0 mg/kg/day group), 5533 (50 mg/kg/day group), and 5561 (250 mg/kg/day group), did show positive evidence of mating and were found to be non-pregnant.

None of the pair wise comparisons showed a difference between a treated group and control when adjusting for the litter size. The litter size was a significant contributor to explaining any differences in endpoints. There were no treatment-related effects apparent for any of the reproductive endpoints: gestation length, litter size, litter weight, ratio live births/litter size, litter sex ratio, number of implantation sites, number of corpora lutea, post-implantation loss, post-natal loss, mating and fertility indices.

## 20 CONCLUSIONS

Oral gavage administration of dimethylsilanediol in a corn oil vehicle to male and female Sprague-Dawley rats at concentrations of up to 500 mg/kg/day for 28 (toxicity group females) or 29 (males) consecutive days was generally well tolerated. For the toxicity group males at 250 and 500 mg/kg/day significant soiling was observed (abdominal region and urogenital soiling). Soiling of the muzzle was a significant abnormal observation in the toxicity group females at 500 mg/kg/day. Both abdominal soiling and urogenital soiling were significant abnormal observations in the reproductive group females at 500 mg/kg/day.

There were no statistically significant differences across exposure groups in the mean body weights on any day for any of the three groups- males, toxicity group females, and reproductive toxicity group females. With respect to body weight gain, 500 mg/kg/day males had a significant decrease in body weight gain during week 4 and in total gain from day 1 to 29. For toxicity group females there was significant decrease in body weight gain during week 3. There were no statistically significant differences in body weight gain for the reproductive group females in any of the treatment groups during any of the measured intervals.

There were no differences in the average daily food consumption across treatment groups for the reproductive group females or the males and toxicity group females for any of the measured time periods.

There were no significant differences of toxicological significance between the control and treatment groups in either sex for the FOB ranked tests. There were no significant differences between either males or toxicity group females and their respective controls for the FOB continuous test and motor activity. There were no treatment-related changes associated with

dimethylsilanediol administration on rat neurobiological function as evaluated with FOB and motor activity parameters.

The significant changes that were noted in hematological parameters and prothrombin times for males and toxicity group females were within or slightly below historical control values, therefore, no changes in hematologic parameters were attributable to the test article. No toxicological significance is given to any statistically identified differences in clinical chemistry since the findings were within or slightly below historical control ranges for this laboratory.

The increased liver weights in males and toxicity group females at 250 and 500 mg/kg/day correlated with the histopathologic finding of centrilobular hypertrophy. There were no other treatment-related differences in organ weights, absolute and relative for males and toxicity group females.

A standard set of protocol-defined tissues was examined for control and 500 mg/kg/day groups. Suspected target tissues were examined for the 50 and 250 mg/kg/day groups. There were three primary effects of the test article observed in the liver, including centrilobular hypertrophy in both sexes, periportal hepatocellular vacuolation (microvesicular lipidosis, females only), and protoporphyrinosis (males only) which was accompanied by chronic inflammation and bile duct hyperplasia. Centrilobular hypertrophy is considered an adaptive change. Hepatic lipidosis, unless severe, is generally considered non-adverse. Hepatic protoporphyrinosis is considered an adverse effect. Follicular cell hypertrophy was observed in the thyroid gland of mid- and high-dose male rats. This is considered an adaptive secondary effect and adverse in the rat, but the mechanism is generally not applicable to species with significant levels of thyroid binding globulin (Capen, *et al.*, 2002). Lung (males and toxicity group females) and prostate gland were considered possible target tissues; however, further examination and inclusion of animals from the 50 and 250 mg/kg/day groups did not support this interpretation.

There were no treatment-related effects apparent for any of the reproductive endpoints: gestation length, litter size, litter weight, ratio live births/litter size, litter sex ratio, number of implantation sites, number of corpora lutea, post-implantation loss, post-natal loss, mating and fertility indices.

Based on the liver results (protoporphyrinosis in males and vacuolation in toxicity group females) observed in this study, the systemic toxicity NOAEL (No-Observed-Adverse-Effect-Level) for dimethylsilanediol in rats via oral administration in corn oil is considered to be 250 mg/kg/day for male and female rats. In the absence of adverse effects on reproductive or developmental parameters in this study, a NOAEL of 500 mg/kg/day is assigned for reproductive and developmental toxicity.

## 21 ARCHIVE

Protocol, amendments and deviations, study authorization documentation, raw data, correspondence, samples/specimens and final report (at minimum) will be retained for five (5) years in the HES Archives, Dow Corning Corporation, 2200 W. Salzburg Road, Auburn, MI 48611. Thereafter, the Sponsor will be contacted for the disposition of the archived material.

The Sponsor will then assume responsibility for the archived materials and any expense for further archiving, disposal and/or shipment.

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## Table 1 - Combined Clinical Observations and Detailed Physical Examination Summary: Male Rats

| Sex - Male | Group 1<br>0 mg/kg/day | | Group 2<br>50 mg/kg/day | | Group 3<br>250 mg/kg/day | | Group 4<br>500 mg/kg/day | |
|---|---|---|---|---|---|---|---|---|
| **Normal** | | | | | | | | |
| No significant clinical observations | 309/10 | | 310/10 | | 270/10 | | 227/10 | |
| **Abnormal** | | | | | | | | |
| Missing Tooth | 0/0 | | 0/0 | | 0/0 | | 4/1 | |
| Skin, Excessive Hair Loss (minimal) | 0/0 | | 0/0 | | 7/1 | | 0/0 | |
| Skin, Scab: Upper Back (Thoracic) (focal) | 0/0 | | 0/0 | | 6/1 | | 0/0 | |
| Soiling: Abdomen, General (yellow) | 0/0 | *** | 0/0 | | 3/2 | | 24/5 | *** |
| Soiling: Chin (clear, red) | 0/0 | | 0/0 | | 0/0 | | 1/1 | |
| Soiling: Muzzle, General (clear, red) | 1/1 | | 0/0 | | 3/3 | | 0/0 | |
| Soiling: Urogenital, General (red, yellow) | 0/0 | *** | 0/0 | | 24/5 | * | 79/10 | *** |
| **Disposition** | | | | | | | | |
| Found Dead | 0/10 | | 0/10 | | 0/10 | | 0/10 | |
| Moribund Sacrifice | 0/10 | | 0/10 | | 0/10 | | 0/10 | |
| Terminal Necropsy | 10/10 | | 10/10 | | 10/10 | | 10/10 | |

Asterisks indicate a significant difference across treatment groups (in the control column) or between control and a treatment group with p-values of * < 0.05, ** < 0.02 or *** < 0.01.

Note: Clinical observations presented as: (number of findings)/(number of animals with the finding).

## Table 2 - Combined Clinical Observations and Detailed Pbysical Examination Summary: Toxicity Group Female Rats

| Sex - Female | Group 1<br>0 mg/kg/day | Group 2<br>50 mg/kg/day | Group 3<br>250 mg/kg/day | Group 4<br>500 mg/kg/day |
|---|---|---|---|---|
| **Normal** | | | | |
| No significant clinical observations | 300/10 | 269/9 [A] | 286/10 | 262/10 |
| **Abnormal finding** | | | | |
| Soiling: Abdomen, General (yellow) | 0/0 | 0/0 | 6/1 | 1/1 |
| Soiling: Nose (red) | 0/0 | 0/0 | 0/0 | 1/1 |
| Soiling: Chin (clear, red) | 0/0 | 1/1 | 0/0 | 20/3 |
| Soiling: Muzzle, General (clear, red) | 0/0 * | 0/0 | 2/2 | 7/4 ** |
| Soiling: Urogenital, General (red, yellow) | 0/0 | 0/0 | 10/2 | 2/2 |
| Respiration, Noisy (wet) | 0/0 | 0/0 | 0/0 | 7/1 |
| Respiration, Rapid | 0/0 | 0/0 | 0/0 | 5/1 |
| **Disposition** | | | | |
| Found Dead | 0/10 | 0/10 | 0/10 | 0/10 |
| Moribund Sacrifice | 0/10 | 0/10 | 0/10 | 0/10 |
| Terminal Necropsy | 10/10 | 9/10 | 10/10 | 10/10 |

[A]Animal D5530 was euthanized on 6-25-2008 due to a gavage error and animal 05504 was moved into the reproductive toxicity female group, 50 mg/kg/day
Asterisks indicate a significant difference across treatment groups (in the control column) or between control and a treatment group with p-values of * < 0.05, ** < 0.02 or *** < 0.01.

Note: Clinical observations presented as: (number of findings)/(number of animals with the finding).

# Table 3 - Combined Clinical Observations and Detailed Physical Examination Summary: Reproductive Group Female Rats

| Sex - Female | Group 1<br>0 mg/kg/day | | Group 2<br>50 mg/kg/day | Group 3<br>250 mg/kg/day | Group 4<br>500 mg/kg/day | |
|---|---|---|---|---|---|---|
| **Normal** | | | | | | |
| No significant clinical observations | 411/10 | | 439/10 | 440/10 | 439/10 | |
| **Abnormal** | | | | | | |
| Palpable Mass 1: Axillary, Left (small) | 2/1 | | 0/0 | 0/0 | 0/0 | |
| Skin, Excessive Hair Loss (minimal, moderate) | 34/2 | | 0/0 | 0/0 | 0/0 | |
| Skin, Scab: Muzzle, Right (focal) | 0/0 | | 0/0 | 3/1 | 0/0 | |
| Skin, Scab: Neck, Left or Right (focal) | 0/0 | | 4/1 | 0/0 | 0/0 | |
| Soiling: Abdomen, General (yellow) | 0/0 | * | 0/0 | 3/1 | 14/7 | *** |
| Soiling: Back, General (yellow) | 0/0 | | 0/0 | 0/0 | 4/1 | |
| Soiling: Nose (red) | 0/0 | | 0/0 | 0/0 | 1/1 | |
| Soiling: Chin (clear, red) | 0/0 | | 0/0 | 0/0 | 2/2 | |
| Soiling: Muzzle, General (clear, red) | 2/2 | | 0/0 | 5/4 | 5/3 | |
| Soiling: Urogenital, General (red, yellow) | 0/0 | *** | 1/1 | 0/0 | 18/6 | *** |
| **Disposition** | | | | | | |
| Found Dead | 0/10 | | 0/10 | 0/10 | 0/10 | |
| Moribund Sacrifice | 0/10 | | 0/10 | 0/10 | 0/10 | |
| Terminal Necropsy | 10/10 | | 10/10 | 10/10 | 10/10 | |

Asterisks indicate a significant difference across treatment groups (in the control column) or between control and a treatment group with p-values of * < 0.05, ** < 0.02 or *** < 0.01.

Note: Clinical observations presented as: (number of findings)/(number of animals with the finding).

## Table 4 - Summary of Weekly Mean Body Weights (grams): Male Rats

| Sex: Male | | Day(s) Relative to Start Date | | | | | |
|---|---|---|---|---|---|---|---|
| | | Day 1 | Day 8 | Day 15 | Day 22 | Day 29 | Day 30 |
| 0 mg/kg/day | Mean | 310.2 | 352.4 | 391.0 | 425.1 | 452.8 | 430.8 |
| | SD | 9.4 | 9.9 | 14.7 | 19.5 | 26.6 | 24.5 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 |
| 50 mg/kg/day | Mean | 310.5 | 352.1 | 388.8 | 421.1 | 444.2 | 421.5 |
| | SD | 9.7 | 13.7 | 20.0 | 31.0 | 32.5 | 32.0 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 |
| 250 mg/kg/day | Mean | 303.3 | 345.4 | 382.9 | 413.8 | 441.8 | 420.2 |
| | SD | 8.7 | 17.6 | 21.2 | 25.3 | 27.3 | 25.1 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 |
| 500 mg/kg/day | Mean | 310.2 | 350.9 | 382.0 | 404.9 | 420.1 | 401.2 |
| | SD | 14.3 | 18.0 | 22.7 | 25.5 | 30.7 | 26.6 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 |

## Table 5 - Summary of Weekly Mean Body Weights (grams): Toxicity Group Female Rats

| Sex: Female | | | Day(s) Relative to Start Date | | | | |
|---|---|---|---|---|---|---|---|
| | | Day 1 | Day 8 | Day 15 | Day 22 | Day 28 | Day 29 |
| 0 mg/kg/day | Mean | 211.4 | 231.3 | 248.5 | 267.9 | 274.7 | 259.6 |
| | SD | 12.5 | 17.8 | 23.6 | 24.7 | 24.6 | 24.1 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 |
| 50 mg/kg/day | Mean | 210.7 | 226.8 | 242.8 | 262.7 | 271.6 | 256.3 |
| | SD | 10.2 | 16.3 | 18.7 | 23.9 | 22.6 | 21.7 |
| | N | 9 | 9 | 9 | 9 | 9 | 9 |
| 250 mg/kg/day | Mean | 211.7 | 231.2 | 249.8 | 265.0 | 270.5 | 258.0 |
| | SD | 14.4 | 13.6 | 17.4 | 19.6 | 15.6 | 16.6 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 |
| 500 mg/kg/day | Mean | 209.0 | 232.3 | 249.2 | 259.2 | 268.8 | 254.5 |
| | SD | 14.0 | 22.6 | 20.4 | 23.9 | 22.2 | 21.5 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 |

## Table 6 - Summary of Weekly Mean Body Weights (grams): Reproductive Group Female Rats

| Sex: Female | | Day 1 | Day 8 | Day 15 | Gestation Day 0 | Gestation Day 7 | Gestation Day 14 | Gestation Day 20 | Post Partum Day 0 | Post Partum Day 4 |
|---|---|---|---|---|---|---|---|---|---|---|
| 0 mg/kg/day | Mean | 210.3 | 232.8 | 251.8 | 259.0 | 292.7 | 331.8 | 416.6 | 322.9 | 340.1 |
| | SD | 7.5 | 9.6 | 9.7 | 14.4 | 11.9 | 18.9 | 43.2 | 16.7 | 13.1 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 9[A] |
| 50 mg/kg/day | Mean | 211.7 | 228.2 | 244.2 | 253.2 | 281.1 | 320.8 | 405.3 | 314.9 | 330.3 |
| | SD | 11.9 | 13.4 | 21.0 | 16.8 | 19.0 | 25.6 | 44.8 | 21.6 | 27.1 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 9[A] |
| 250 mg/kg/day | Mean | 216.2 | 236.5 | 255.1 | 261.4 | 289.4 | 328.6 | 408.8 | 317.1 | 332.5 |
| | SD | 12.1 | 14.1 | 14.1 | 12.9 | 19.5 | 27.9 | 56.7 | 22.8 | 24.6 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 9[A] |
| 500 mg/kg/day | Mean | 210.4 | 231.5 | 244.9 | 255.2 | 286.4 | 317.9 | 396.8 | 299.3 | 324.3 |
| | SD | 11.0 | 16.4 | 20.7 | 21.6 | 18.7 | 24.0 | 38.3 | 21.1 | 25.0 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

[A]Data of non-pregnant female(s) with positive evidence of mating not included in calculations.

## Table 7 - Summary of Weekly Mean Body Weight Gain (grams): Male Rats

| Sex: Male | | Week 1 | Week 2 | Week 3 | Week 4 | Total by Day 29 |
|---|---|---|---|---|---|---|
| 0 mg/kg/day | Mean | 42.2 | 38.6 | 34.2 | 27.63 * | 142.6 * |
| | SD | 6.1 | 8.1 | 7.7 | 9.4 | 25.0 |
| | N | 10 | 10 | 10 | 10.0 | 10.0 |
| 50 mg/kg/day | Mean | 41.6 | 36.8 | 32.3 | 23.1 | 133.7 |
| | SD | 8.5 | 9.6 | 13.3 | 4.1 | 28.4 |
| | N | 10 | 10 | 10 | 10.0 | 10.0 |
| 250 mg/kg/day | Mean | 42.0 | 37.5 | 31.0 | 28.0 | 138.5 |
| | SD | 13.6 | 8.9 | 10.2 | 6.9 | 23.0 |
| | N | 10 | 10 | 10 | 10.0 | 10.0 |
| 500 mg/kg/day | Mean | 40.7 | 31.1 | 22.9 | 15.15 * | 109.91 ** |
| | SD | 8.4 | 7.5 | 7.5 | 19.3 | 24.5 |
| | N | 10 | 10 | 10 | 10.0 | 10.0 |

Note: Asterisks indicate a significant difference across treatment groups (in the control column) or between control and a treatment group with p-values of * <0.05, ** <0.02 or *** <0.01.

## Table 8 - Summary of Weekly Mean Body Weight Gain (grams): Toxicity Group Female Rats

| Sex: Female | | Week 1 | Week 2 | Week 3 | Week 4 | Total by Day 28 |
|---|---|---|---|---|---|---|
| 0 mg/kg/day | Mean | 19.9 | 17.2 | 19.39 ** | 6.8 | 63.3 |
| | SD | 7.0 | 7.3 | 7.6 | 4.6 | 15.3 |
| | N | 10 | 10 | 10 | 10 | 10 |
| 50 mg/kg/day | Mean | 16.1 | 16.0 | 19.8 | 9.0 | 60.9 |
| | SD | 7.2 | 4.6 | 7.3 | 3.6 | 15.0 |
| | N | 9 | 9 | 9 | 9 | 9 |
| 250 mg/kg/day | Mean | 19.5 | 18.6 | 15.1 | 5.5 | 58.7 |
| | SD | 4.0 | 6.6 | 7.2 | 5.7 | 9.2 |
| | N | 10 | 10 | 10 | 10 | 10 |
| 500 mg/kg/day | Mean | 23.3 | 16.9 | 9.97 ** | 9.7 | 59.8 |
| | SD | 10.4 | 4.6 | 5.7 | 5.6 | 9.9 |
| | N | 10 | 10 | 10 | 10 | 10 |

Note: Asterisks indicate a significant difference across treatment groups (in the control column) or between control and a treatment group with p-values of * <0.05, ** <0.02 or *** <0.01.

## Table 9 - Summary of Weekly Mean Body Weight Gain (grams): Reproductive Group Female Rats

| Sex: Female | | Week 1 Pre Mating | Week 2 Pre Mating | Gestation Week 1 | Gestation Week 2 | Gestation Week 3 | 4 days Post Partum | Overall Weight Gain |
|---|---|---|---|---|---|---|---|---|
| 0 mg/kg/day | Mean | 22.5 | 19.0 | 33.7 | 39.1 | 84.8 | 15.0 | 129.3 |
| | SD | 5.4 | 4.6 | 5.3 | 11.1 | 27.7 | 7.8 | 11.1 |
| | N | 10 | 10 | 10 | 10 | 10 | 9 | 9[A] |
| 50 mg/kg/day | Mean | 16.6 | 15.9 | 27.9 | 39.8 | 84.4 | 15.6 | 118.8 |
| | SD | 4.0 | 8.5 | 8.0 | 9.9 | 26.4 | 14.6 | 21.1 |
| | N | 10 | 10 | 10 | 10 | 10 | 9 | 9[A] |
| 250 mg/kg/day | Mean | 20.3 | 18.7 | 28.0 | 39.2 | 80.2 | 11.8 | 115.7 |
| | SD | 8.1 | 7.4 | 9.9 | 11.1 | 31.0 | 7.8 | 16.9 |
| | N | 10 | 10 | 10 | 10 | 10 | 9 | 9[A] |
| 500 mg/kg/day | Mean | 21.0 | 13.4 | 31.2 | 31.4 | 78.9 | 25.0 | 113.9 |
| | SD | 7.8 | 6.0 | 5.4 | 7.5 | 23.4 | 10.6 | 16.6 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

[A]Data of non-pregnant female(s) with positive evidence of mating not included in calculations.

## Table 10 - Summary of Weekly Mean Food Consumption (grams/animal/day): Male Rats

| Sex: Male | | Week 1 | Week 2 | Total (g) |
|---|---|---|---|---|
| 0 mg/kg/day | Mean | 25.9 | 24.7 * | 353.6 |
| | SD | 1.9 | 2.1 | 27.4 |
| | N | 10 | 10 | 10 |
| 50 mg/kg/day | Mean | 26.0 | 25.4 | 359.1 |
| | SD | 2.1 | 2.5 | 31.2 |
| | N | 10 | 10 | 10 |
| 250 mg/kg/day | Mean | 25.3 | 24.9 | 351.7 |
| | SD | 2.6 | 2.2 | 31.0 |
| | N | 10 | 10 | 10 |
| 500 mg/kg/day | Mean | 23.7 | 22.6 | 324.5 |
| | SD | 2.2 | 2.1 | 29.5 |
| | N | 10 | 10 | 10 |

Note: Asterisks indicate a significant difference across treatment groups (in the control column) or between control and a treatment group with p-values of * <0.05, ** <0.02 or *** < 0.01.

## Table 11 - Summary of Weekly Mean Food Consumption (grams/animal/day): Toxicity Group Female Rats

| Sex: Female | | Week 1 | Week 2 | Week 3 | Week 4 | Total (grams) |
|---|---|---|---|---|---|---|
| 0 mg/kg/day | Mean | 18.8 | 19.2 | 19.6 | 17.5 | 507.6 |
| | SD | 3.2 | 2.6 | 2.6 | 3.1 | 72.9 |
| | N | 10 | 10 | 10 | 10 | 10 |
| 50 mg/kg/day | Mean | 17.1 | 17.5 | 18.0 | 17.0 | 470.6 |
| | SD | 2.4 | 1.6 | 2.0 | 1.7 | 48.7 |
| | N[A] | 9 | 9 | 9 | 9 | 9 |
| 250 mg/kg/day | Mean | 17.7 | 18.6 | 17.8 | 16.6 | 478.3 |
| | SD | 1.5 | 2.0 | 1.9 | 1.7 | 45.0 |
| | N | 10 | 10 | 10 | 10 | 10 |
| 500 mg/kg/day | Mean | 17.3 | 18.5 | 17.9 | 16.4 | 474.2 |
| | SD | 2.2 | 1.9 | 1.5 | 1.9 | 43.6 |
| | N | 10 | 10 | 10 | 10 | 10 |

[A]Animal D5530 was euthanized on 6-25-2008 and animal D5504 was moved into the reproductive toxicity female group, 50 mg/kg/day

## Table 12 - Summary of Weekly Mean Food Consumption (grams/animal/day): Reproductive Group Female Rats

| Sex: Female | | Pre-mating Week 1 | Pre-mating Week 2 | Gestation Week 1 | Gestation Week 2 | Gestation Week 3 | Post Partum |
|---|---|---|---|---|---|---|---|
| 0 mg/kg/day | | | | | | | |
| | Mean | 18.2 | 18.6 | 19.3 | 20.6 | 22.7 | 35.0 |
| | SD | 1.4 | 1.0 | 1.4 | 1.5 | 2.2 | 3.3 |
| | N | 10 | 10 | 10 | 10 | 10 | 9[A] |
| 50 mg/kg/day | Mean | 18.6 | 18.7 | 18.7 | 20.7 | 23.1 | 34.9 |
| | SD | 2.0 | 2.5 | 2.4 | 2.1 | 3.0 | 5.5 |
| | N | 10 | 10 | 10 | 10 | 10 | 9[A] |
| 250 mg/kg/day | Mean | 19.4 | 19.9 | 18.1 | 19.6 | 22.5 | 32.2 |
| | SD | 1.5 | 1.8 | 2.3 | 3.2 | 4.1 | 5.5 |
| | N | 10 | 10 | 10 | 10 | 10 | 9[A] |
| 500 mg/kg/day | Mean | 17.6 | 17.4 | 18.0 | 18.8 | 22.2 | 32.5 |
| | SD | 2.7 | 2.1 | 2.1 | 1.9 | 2.9 | 7.3 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 |

[A]Data of non-pregnant female(s) with positive evidence of mating not included in calculations.

## Table 13 - Summary of Functional Observation Battery Ranked/Categorical Incidence: Male Rats (Baseline and Treated)

| | Baseline | | | | Treated | | | |
|---|---|---|---|---|---|---|---|---|
| **Dose Group** | **1** | **2** | **3** | **4** | **1** | **2** | **3** | **4** |
| Number of Animals Examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Resistance to Removal** | | | | | | | | |
| (3) Moderate; actively avoids capture but is not aggressive | 10 | 10 | 10 | 8 | 10 | 10 | 10 | 10 |
| (4) Pronounced; actively avoids capture and/or is mildly aggressive | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| (5) Exaggerated; very difficult to capture and is very aggressive (i.e. tries to bite) | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| **Palpebral Closure** | | | | | | | | |
| (3) Open | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Pupil Reactivity** | | | | | | | | |
| (3) dilated, briskly reactive pupil | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Pupil Size** | | | | | | | | |
| (3) Normal pupil size | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Lacrimation** | | | | | | | | |
| (3) Glistening cornea | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Salivation** | | | | | | | | |
| (3) glistening oral cavity/lips, no wetness | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Muscle Tone** | | | | | | | | |
| (3) moderate; animal is neither very relaxed nor tense | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day

## Table 13 - Summary of Functional Observation Battery Ranked/Categorical Incidence: Male Rats (Baseline and Treated) Cont.

| | Baseline | | | | Treated | | | |
|---|---|---|---|---|---|---|---|---|
| **Dose Group** | **1** | **2** | **3** | **4** | **1** | **2** | **3** | **4** |
| Number of Animals Examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Extensor Thrust** | | | | | | | | |
| (3) moderate; clearly detectable | 10 | 10 | 10 | 10 | 9 | 10 | 10 | 9 |
| (4) Pronounced; pushes vigorously | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| **Reactivity to Handling** | | | | | | | | |
| (3) moderate struggling with little or no vocalization | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Level of Activity** | | | | | | | | |
| (2) minimal, inactive more than 50% of the time | 0 | 1 | 0 | 1 | 3 | 4 | 3 | 5 |
| (3) moderate, inactive less than 50% of the time | 10 | 9 | 10 | 9 | 7 | 6 | 7 | 5 |
| **Response to Noise** | * | | | | | | | |
| (3) moderate; clear movement of the head, neck, ears and possibly front shoulders/upper body | 10 | 10 | 8 | 7 | 7 | 9 | 8 | 9 |
| (4) pronounced; clear movement of head, neck and ears, plus clear movement of whole body | 0 | 0 | 2 | 3 | 3 | 1 | 2 | 0 |
| (5) exaggerated; whole body response to stimulus, more intense than "pronounced"; includes whole body | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| **Response to Touch** | | | | | | | | |
| (3) moderate; spontaneously lifts tail when touched | 10 | 9 | 10 | 8 | 10 | 10 | 10 | 9 |
| (4) Pronounced; spontaneously lifts tail and acts startled | 0 | 1 | 0 | 2 | 0 | 0 | 0 | 1 |

Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day

*Asterisks indicate a significant difference across treatment groups (in the control column) or between control and a treatment group with p-values of * < 0.05, ** < 0.02 or *** < 0.01.

**Table 13 - Summary of Functional Observation Battery Ranked/Categorical Incidence: Male Rats (Baseline and Treated) Cont.**

| | Baseline | | | | Treated | | | |
|---|---|---|---|---|---|---|---|---|
| **Dose Group** | **1** | **2** | **3** | **4** | **1** | **2** | **3** | **4** |
| Number of Animals Examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Response to Tail Pinch** | | | | | | | | |
| (2) minimal; animal flinches and may vocalize | 1 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| (3) moderate; animal flinches, moves rapidly and/or vocalizes | 9 | 10 | 10 | 10 | 8 | 10 | 10 | 10 |
| **Gait Evaluation** | | | | | | | | |
| (1) smooth and coordinated gait | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Urination** | | | | | | | | |
| (1) no drops of urine | 3 | 1 | 4 | 2 | 1 | 1 | 0 | 1 |
| (2) minimal; a few (1-4) small drops or a small pool (~1 cm) | 3 | 4 | 3 | 5 | 3 | 0 | 0 | 2 |
| (3) moderate; a few (1-4) small pools or a moderate pool (2-3 cm) | 0 | 2 | 2 | 0 | 1 | 1 | 4 | 2 |
| (4) pronounced; a few (1-4) moderate pools or a large pool (4-5 cm) | 1 | 1 | 0 | 0 | 3 | 1 | 2 | 2 |
| (5) Exaggerated; >4 moderate pools or single pool >5 cm. | 3 | 2 | 1 | 3 | 2 | 7 | 4 | 3 |

Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day

**Table 13 - Summary of Functional Observation Battery Ranked/Categorical Incidence: Male Rats (Baseline and Treated) Cont.**

| | Baseline | | | | Treated | | | |
|---|---|---|---|---|---|---|---|---|
| **Dose Group** | **1** | **2** | **3** | **4** | **1** | **2** | **3** | **4** |
| Number of Animals Examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Defecation** | | | | | *** | | | * |
| (1) no pellets voided | 5 | 7 | 5 | 3 | 4 | 3 | 1 | 1 |
| (2) minimal; 1 or 2 pellets voided | 4 | 1 | 3 | 5 | 3 | 4 | 5 | 1 |
| (3) moderate ; 3 pellets voided | 0 | 1 | 2 | 1 | 1 | 1 | 3 | 2 |
| (4) pronounced; 4 pellets voided | 0 | 1 | 0 | 0 | 2 | 1 | 0 | 3 |
| (5) Exaggerated; 5 or more pellets voided | 1 | 0 | 0 | 1 | 0 | 1 | 1 | 3 |
| **Categorical Observations** | | | | | | | | |
| No Abnormalities Detected | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 8 |
| Soiling Perineal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |

Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day

*Asterisks indicate a significant difference across treatment groups (in the control column) or between control and a treatment group with p-values of * < 0.05, ** < 0.02 or *** < 0.01.

## Table 14 - Summary of Functional Observation Battery Ranked/Categorical Incidence: Toxicity Group Female Rats (Baseline and Treated)

| | Baseline | | | | Treated | | | |
|---|---|---|---|---|---|---|---|---|
| **Dose Group** | **1** | **2** | **3** | **4** | **1** | **2** | **3** | **4** |
| Number of Animals Examined | 10 | 9[A] | 10 | 10 | 10 | 9 | 10 | 10 |
| **Resistance to Removal** | | | | | | | | |
| (2) Minimally avoids capture but is not aggressive | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| (3) Moderate; actively avoids capture but is not aggressive | 10 | 7 | 10 | 10 | 9 | 9 | 10 | 10 |
| (4) Pronounced; actively avoids capture and/or is mildly aggressive | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Palpebral Closure** | | | | | | | | |
| (3) Open | 10 | 9 | 10 | 10 | 10 | 9 | 10 | 10 |
| **Pupil Reactivity** | | | | | | | | |
| (3) dilated, briskly reactive pupil | 10 | 9 | 10 | 10 | 10 | 9 | 10 | 10 |
| **Pupil Size** | | | | | | | | |
| (3) Normal pupil size | 10 | 9 | 10 | 10 | 10 | 9 | 10 | 10 |
| **Lacrimation** | | | | | | | | |
| (3) Glistening cornea | 10 | 9 | 10 | 10 | 10 | 9 | 10 | 10 |
| **Salivation** | | | | | | | | |
| (3) glistening oral cavity/lips, no wetness | 10 | 9 | 10 | 10 | 10 | 9 | 10 | 10 |

Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day
A - Animal excluded from statistical analysis due to being moved from the toxicology group to the reproductive group after baseline testing.

**Table 14 - Summary of Functional Observation Battery Ranked/Categorical Incidence: Toxicity Group Female Rats (Baseline and Treated) Cont.**

| | Baseline | | | | Treated | | | |
|---|---|---|---|---|---|---|---|---|
| **Dose Group** | **1** | **2** | **3** | **4** | **1** | **2** | **3** | **4** |
| Number of Animals Examined | 10 | 9[A] | 10 | 10 | 10 | 9 | 10 | 10 |
| **Muscle Tone** | | | | | | | | |
| (3) moderate; animal is neither very relaxed nor tense | 10 | 9 | 10 | 10 | 10 | 9 | 10 | 10 |
| **Extensor Thrust** | | | | | | | | |
| (3) moderate; clearly detectable | 10 | 9 | 10 | 10 | 10 | 9 | 10 | 10 |
| **Reactivity to Handling** | | | | | | | | |
| (3) moderate struggling with little or no vocalization | 9 | 8 | 10 | 10 | 10 | 9 | 10 | 10 |
| (4) pronounced struggling, animal may vocalize | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Level of Activity** | | | | | | | | |
| (2) minimal, inactive more than 50% of the time | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| (3) moderate, inactive less than 50% of the time | 10 | 9 | 10 | 10 | 9 | 8 | 10 | 10 |
| (4) pronounced; leaves circle, occasional inactivity | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |

Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day
A - Animal excluded from statistical analysis due to being moved from the toxicology group to the reproductive group after baseline testing.

## Table 14 - Summary of Functional Observation Battery Ranked/Categorical Incidence: Toxicity Group Female Rats (Baseline and Treated) Cont.

| | Baseline | | | | Treated | | | |
|---|---|---|---|---|---|---|---|---|
| **Dose Group** | **1** | **2** | **3** | **4** | **1** | **2** | **3** | **4** |
| Number of Animals Examined | 10 | 9[A] | 10 | 10 | 10 | 9 | 10 | 10 |
| **Response to Noise** | | | | | | | | |
| (3) moderate; clear movement of the head, neck, ears and possibly front shoulders/upper body | 8 | 8 | 9 | 8 | 6 | 4 | 8 | 6 |
| (4) pronounced; clear movement of head, neck and ears, plus clear movement of whole body | 2 | 1 | 1 | 2 | 4 | 5 | 2 | 3 |
| (5) exaggerated; whole body response to stimulus, more intense than "pronounced"; includes whole body | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| **Response to Touch** | | | | | | | | |
| (3) moderate; spontaneously lifts tail when touched | 10 | 8 | 9 | 10 | 10 | 9 | 10 | 10 |
| (4) Pronounced; spontaneously lifts tail and acts startled | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 |
| **Response to Tail Pinch** | | | | | | | | |
| (2) minimal; animal flinches and may vocalize | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| (3) moderate; animal flinches, moves rapidly and/or vocalizes | 10 | 9 | 9 | 10 | 10 | 9 | 10 | 10 |
| **Gait Evaluation** | | | | | | | | |
| (1) smooth and coordinated gait | 10 | 9 | 10 | 10 | 10 | 9 | 10 | 10 |

Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day
A - Animal excluded from statistical analysis due to being moved from the toxicology group to the reproductive group after baseline testing.

## Table 14 - Summary of Functional Observation Battery Ranked/Categorical Incidence: Toxicity Group Female Rats (Baseline and Treated) Cont.

| | Baseline | | | | Treated | | | |
|---|---|---|---|---|---|---|---|---|
| **Dose Group** | **1** | **2** | **3** | **4** | **1** | **2** | **3** | **4** |
| Number of Animals Examined | 10 | 9[A] | 10 | 10 | 10 | 9 | 10 | 10 |
| **Urination** | | | | | | | | |
| (1) no drops of urine | 5 | 2 | 1 | 2 | 1 | 2 | 4 | 1 |
| (2) minimal; a few (1-4) small drops or a small pool (~1 cm) | 4 | 6 | 6 | 6 | 4 | 4 | 4 | 7 |
| (3) moderate; a few (1-4) small pools or a moderate pool (2-3 cm) | 0 | 0 | 3 | 2 | 4 | 3 | 1 | 1 |
| (4) pronounced; a few (1-4) moderate pools or a large pool (4-5 cm) | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| (5) Exaggerated; >4 moderate pools or single pool >5 cm. | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 0 |
| **Defecation** | | | | | | | | |
| (1) no pellets voided | 8 | 9 | 9 | 9 | 7 | 6 | 8 | 6 |
| (2) minimal; 1 or 2 pellets voided | 2 | 0 | 0 | 1 | 2 | 0 | 2 | 1 |
| (3) moderate ; 3 pellets voided | 0 | 0 | 0 | 0 | 1 | 2 | 0 | 1 |
| (4) pronounced; 4 pellets voided | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| (5) Exaggerated; 5 or more pellets voided | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 1 |
| **Categorical Observations** | | | | | | | | |
| No Abnormalities Detected | 10 | 10 | 10 | 10 | 10 | 9 | 9 | 10 |
| Soiling Abdominal, Soiling Perineal | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |

Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day
A - Animal excluded from statistical analysis due to being moved from the toxicology group to the reproductive group after baseline testing.

## Table 15 - Summary of Functional Observation Battery Continuous Data: Male Rats (Baseline and Treated)

| | | Baseline | | | | Treated | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group Sex | | Rectal Temperature (°C) | Hindlimb Grip Strength (g) | Forelimb Grip Strength (g) | Landing Foot Splay (cm) | Rectal Temperature (°C) | Hindlimb Grip Strength (g) | Forelimb Grip Strength (g) | Landing Foot Splay (cm) |
| 1m | Mean | 37.5 | 814.5 | 818.5 | 11.5 | 38.0 | 1249.5 | 1077.0 | 13.2 |
| | S.D. | 0.5 | 145.8 | 143.0 | 2.0 | 0.5 | 126.7 | 258.8 | 2.2 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| 2m | Mean | 37.6 | 750.9 | 809.3 | 11.7 | 38.0 | 1222.0 | 1111.7 | 11.9 |
| | S.D. | 0.5 | 114.9 | 141.7 | 2.4 | 0.4 | 150.8 | 188.8 | 1.5 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| 3m | Mean | 37.7 | 704.8 | 745.2 | 12.7 | 37.9 | 1235.5 | 1022.2 | 11.8 |
| | S.D. | 0.3 | 130.2 | 90.2 | 2.5 | 0.2 | 165.5 | 268.9 | 1.5 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| 4m | Mean | 37.7 | 716.4 | 813.5 | 11.9 | 37.8 | 1065.2 | 992.5 | 12.0 |
| | S.D. | 0.4 | 111.5 | 166.4 | 1.4 | 0.4 | 180.2 | 163.5 | 1.5 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day

## Table 16 – Summary of Functional Observation Battery Continuous Data: Toxicity Group Female Rats (Baseline and Treated)

| | | Baseline | | | | Treated | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group Sex | | Rectal Temperature (°C) | Hindlimb Grip Strength (g) | Forelimb Grip Strength (g) | Landing Foot Splay (cm) | Rectal Temperature (°C) | Hindlimb Grip Strength (g) | Forelimb Grip Strength (g) | Landing Foot Splay (cm) |
| 1f | Mean | 38.1 | 693.2 | 721.8 | 10.8 | 38.2 | 1005.5 | 866.0 | 9.8 |
| | S.D. | 0.6 | 119.1 | 69.6 | 1.0 | 0.4 | 138.2 | 170.6 | 1.5 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| 2f | Mean | 38.0 | 649.4 | 737.2 | 10.6 | 38.4 | 1019.3 | 975.9 | 11.4 |
| | S.D. | 0.3 | 101.6 | 91.7 | 2.2 | 0.4 | 105.7 | 145.6 | 2.0 |
| | N* | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| 3f | Mean | 37.9 | 681.5 | 721.3 | 10.9 | 38.4 | 1108.3 | 992.5 | 10.1 |
| | S.D. | 0.4 | 107.7 | 86.4 | 1.8 | 0.3 | 193.1 | 237.3 | 1.3 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| 4f | Mean | 38.0 | 719.0 | 743.7 | 10.9 | 38.5 | 985.7 | 990.2 | 10.5 |
| | S.D. | 0.4 | 163.2 | 81.0 | 1.9 | 0.3 | 225.6 | 178.3 | 1.9 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day
* Animal excluded from statistical analysis due to being moved from the toxicology group to the reproductive group after baseline testing.

## Table 17 - Summary of Motor Activity: Male Rats (Baseline and Treated)

| | | Baseline | | | | Treated | | | |
|---|---|---|---|---|---|---|---|---|---|
| Interval | Group/Sex | 1m | 2m | 3m | 4m | 1m | 2m | 3m | 4m |
| (8 minutes) | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| 1 | Mean | 238 | 259 | 212 | 221 | 225 | 248 | 191 | 229 |
| | S.D. | 39 | 58 | 33 | 48 | 46 | 83 | 44 | 31 |
| 2 | Mean | 174 | 218 | 179 | 156 | 173 | 172 | 140 | 141 |
| | S.D. | 54 | 55 | 46 | 49 | 57 | 65 | 56 | 34 |
| 3 | Mean | 141 | 151 | 131 | 115 | 91 | 134 | 102 | 100 |
| | S.D. | 58 | 68 | 62 | 77 | 26 | 59 | 35 | 40 |
| 4 | Mean | 109 | 132 | 112 | 80 | 50 | 54 | 66 | 53 |
| | S.D. | 53 | 83 | 80 | 81 | 32 | 49 | 40 | 27 |
| 5 | Mean | 98 | 85 | 58 | 35 | 40 | 65 | 52 | 48 |
| | S.D. | 73 | 83 | 54 | 52 | 29 | 75 | 40 | 37 |
| 6 | Mean | 69 | 32 | 55 | 23 | 49 | 51 | 45 | 45 |
| | S.D. | 67 | 46 | 58 | 40 | 41 | 51 | 37 | 55 |
| 7 | Mean | 35 | 27 | 14 | 19 | 51 | 44 | 43 | 19 |
| | S.D. | 38 | 45 | 23 | 39 | 49 | 30 | 37 | 27 |
| 8 | Mean | 13 | 3 | 39 | 0 | 31 | 37 | 30 | 9 |
| | S.D. | 31 | 9 | 48 | 1 | 34 | 35 | 35 | 21 |
| 9 | Mean | 15 | 3 | 34 | 1 | 26 | 45 | 22 | 6 |
| | S.D. | 30 | 8 | 51 | 1 | 39 | 38 | 39 | 8 |
| 10 | Mean | 14 | 1 | 6 | 2 | 31 | 23 | 26 | 23 |
| | S.D. | 44 | 2 | 15 | 5 | 34 | 31 | 34 | 31 |
| Total | Mean | 906 | 911 | 840 | 651 | 766 | 873 | 716 | 673 |
| | S.D. | 290 | 348 | 275 | 286 | 222 | 323 | 210 | 153 |

Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day

## Table 18 - Summary of Motor Activity: Toxicity Group Female Rats (Baseline and Treated)

| | | Baseline | | | | Treated | | | |
|---|---|---|---|---|---|---|---|---|---|
| Interval | Group/Sex | 1f | 2f | 3f | 4f | 1f | 2f | 3f | 4f |
| (8 minutes) | N* | 10 | 9 | 10 | 10 | 10 | 9 | 10 | 10 |
| 1 | Mean | 252 | 254 | 268 | 232 | 246 | 203 | 211 | 213 |
| | S.D | 46 | 44 | 40 | 25 | 33 | 44 | 39 | 34 |
| 2 | Mean | 191 | 172 | 189 | 181 | 191 | 166 | 162 | 154 |
| | S.D | 41 | 30 | 46 | 22 | 62 | 44 | 42 | 30 |
| 3 | Mean | 156 | 105 | 131 | 137 | 150 | 122 | 146 | 127 |
| | S.D. | 58 | 70 | 34 | 47 | 63 | 43 | 44 | 40 |
| 4 | Mean | 120 | 75 | 110 | 84 | 116 | 101 | 96 | 98 |
| | S.D. | 60 | 54 | 29 | 54 | 73 | 70 | 49 | 43 |
| 5 | Mean | 115 | 53 | 80 | 66 | 126 | 89 | 98 | 75 |
| | S.D. | 75 | 53 | 65 | 54 | 78 | 54 | 61 | 40 |
| 6 | Mean | 100 | 44 | 37 | 47 | 120 | 64 | 72 | 70 |
| | S.D. | 65 | 44 | 72 | 58 | 115 | 44 | 51 | 35 |
| 7 | Mean | 116 | 37 | 43 | 38 | 97 | 51 | 88 | 77 |
| | S.D. | 83 | 42 | 67 | 48 | 63 | 58 | 45 | 42 |
| 8 | Mean | 91 | 8 | 33 | 29 | 109 | 53 | 51 | 59 |
| | S.D. | 50 | 21 | 38 | 47 | 64 | 52 | 35 | 37 |
| 9 | Mean | 66 | 17 | 65 | 19 | 83 | 52 | 62 | 74 |
| | S.D. | 78 | 33 | 90 | 31 | 46 | 41 | 56 | 45 |
| 10 | Mean | 51 | 2 | 57 | 8 | 93 | 70 | 49 | 50 |
| | S.D. | 58 | 5 | 95 | 21 | 61 | 47 | 42 | 14 |
| Total | Mean | 1257 | 766 | 1013 | 840 | 1330 | 971 | 1034 | 996 |
| | S.D. | 468 | 269 | 402 | 273 | 457 | 338 | 303 | 160 |

Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day
* Animal excluded from statistical analysis due to being moved from the toxicology group to the reproductive group after baseline testing.

## Table 19 - Summary of Mean Hematology Data: Male Rats

| Sex: Male | | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
|---|---|---|---|---|---|
| WBC ($10^3$/uL) | Mean | 8.18 | 8.80 | 7.87 | 7.13 |
| | SD | 2.19 | 2.35 | 1.92 | 1.16 |
| | N | 10 | 10 | 10 | 10 |
| RBC *[1] ($10^6$/uL) | Mean | 7.462 | 7.682 | 7.362 | 7.320 |
| | SD | 0.280 | 0.261 | 0.271 | 0.279 |
| | N | 10 | 10 | 10 | 10 |
| HGB **[2] (g/dL) | Mean | 14.24 | 14.58 | 14.09 | 13.49 **[3] |
| | SD | 0.38 | 0.43 | 0.40 | 0.68 |
| | N | 10 | 10 | 10 | 10 |
| HCT **[2] (%) | Mean | 41.41 | 42.17 | 41.35 | 39.63 ** |
| | SD | 0.98 | 1.40 | 1.16 | 1.92 |
| | N | 10 | 10 | 10 | 10 |
| MCV (fL) | Mean | 55.55 | 54.92 | 56.20 | 54.14 |
| | SD | 1.97 | 1.37 | 1.59 | 1.78 |
| | N | 10 | 10 | 10 | 10 |
| MCH **[2] (pg) | Mean | 19.12 | 18.97 | 19.17 | 18.41 **[3] |
| | SD | 0.46 | 0.40 | 0.57 | 0.47 |
| | N | 10 | 10 | 10 | 10 |
| MCHC (g/dL) | Mean | 34.41 | 34.56 | 34.11 | 34.04 |
| | SD | 0.68 | 0.33 | 0.47 | 0.54 |
| | N | 10 | 10 | 10 | 10 |
| PLT ($10^3$/uL) | Mean | 970.20 | 1015.40 | 908.40 | 937.90 |
| | SD | 65.18 | 101.85 | 137.00 | 161.98 |
| | N | 10 | 10 | 10 | 10 |

[1] [Group Factor 1 Way ANOVA: * - 5% significance level]
[2] [Group Factor 1 Way ANOVA: ** - 1% significance level]
[3] [** - 1% significance level]
[4] [* - 5% significance level]

## Table 20 - Summary of Mean Hematology Data: Toxicity Group Female Rats

| Sex: Female | | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
|---|---|---|---|---|---|
| WBC ($10^3$/uL) | Mean | 5.06 | 5.48 | 5.47 | 5.57 |
| | SD | 1.85 | 1.62 | 1.62 | 1.41 |
| | N | 9 | 9 | 9 | 10 |
| RBC ($10^6$/uL) | Mean | 7.399 | 7.394 | 7.434 | 7.327 |
| | SD | 0.323 | 0.382 | 0.292 | 0.139 |
| | N | 9 | 9 | 9 | 10 |
| HGB **1 (g/dL) | Mean | 14.52 | 14.50 | 14.16 | 13.92 **2 |
| | SD | 0.40 | 0.42 | 0.47 | 0.32 |
| | N | 9 | 9 | 9 | 10 |
| HCT (%) | Mean | 43.01 | 43.12 | 42.22 | 42.02 |
| | SD | 1.14 | 1.24 | 1.74 | 1.07 |
| | N | 9 | 9 | 9 | 10 |
| MCV (fL) | Mean | 58.22 | 58.41 | 56.82 | 57.34 |
| | SD | 2.40 | 2.35 | 1.75 | 1.59 |
| | N | 9 | 9 | 9 | 10 |
| MCH *3 (pg) | Mean | 19.66 | 19.67 | 19.06 | 19.00 |
| | SD | 0.76 | 0.72 | 0.58 | 0.44 |
| | N | 9 | 9 | 9 | 10 |
| MCHC **1 (g/dL) | Mean | 33.78 | 33.68 | 33.52 | 33.13 **2 |
| | SD | 0.36 | 0.30 | 0.37 | 0.36 |
| | N | 9 | 9 | 9 | 10 |
| PLT ($10^3$/uL) | Mean | 1183.78 | 1185.11 | 1182.00 | 1113.00 |
| | SD | 106.41 | 109.47 | 173.29 | 121.03 |
| | N | 9 | 9 | 9 | 10 |

*[Group Factor 1 Way ANOVA: ** - 1% significance level]
*[** - 1% significance level]
*[Group Factor 1 Way ANOVA: * - 5% significance level]

## Table 21 - Summary of Mean Hematology Differential Data: Male Rats

| Sex: Male | | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
|---|---|---|---|---|---|
| Neutro (%) | Mean | 14.72 | 18.14 | 14.72 | 14.00 |
| | SD | 5.19 | 19.61 | 6.38 | 4.43 |
| | N | 10 | 10 | 10 | 10 |
| Abs Neut ($10^3$/uL) | Mean | 1.1668 | 1.9049 | 1.2006 | 0.9903 |
| | SD | 0.4109 | 2.9632 | 0.6824 | 0.3395 |
| | N | 10 | 10 | 10 | 10 |
| Lymph (%) | Mean | 77.56 | 74.56 | 77.00 | 78.39 |
| | SD | 5.24 | 20.03 | 7.30 | 5.52 |
| | N | 10 | 10 | 10 | 10 |
| Abs Lymph ($10^3$/uL) | Mean | 6.3860 | 6.2580 | 6.0170 | 5.6020 |
| | SD | 2.0440 | 1.8431 | 1.4169 | 1.1274 |
| | N | 10 | 10 | 10 | 10 |
| Mono (%) | Mean | 5.34 | 4.91 | 5.86 | 5.50 |
| | SD | 2.07 | 1.94 | 1.45 | 2.82 |
| | N | 10 | 10 | 10 | 10 |
| Abs Mono ($10^3$/uL) | Mean | 0.4237 | 0.4386 | 0.4591 | 0.3746 |
| | SD | 0.1938 | 0.2266 | 0.1712 | 0.1811 |
| | N | 10 | 10 | 10 | 10 |
| Eosin (%) | Mean | 1.62 | 1.67 | 1.62 | 1.49 |
| | SD | 0.57 | 0.73 | 0.64 | 0.57 |
| | N | 10 | 10 | 10 | 10 |
| Abs Eosin ($10^3$/uL) | Mean | 0.1270 | 0.1389 | 0.1331 | 0.1064 |
| | SD | 0.0422 | 0.0491 | 0.0795 | 0.0440 |
| | N | 10 | 10 | 10 | 10 |
| Baso (%) | Mean | 0.76 | 0.68 | 0.83 | 0.60 |
| | SD | 0.41 | 0.34 | 0.41 | 0.51 |
| | N | 10 | 10 | 10 | 10 |
| Abs Baso ($10^3$/uL) | Mean | 0.0625 | 0.0606 | 0.0624 | 0.0408 |
| | SD | 0.0355 | 0.0326 | 0.0287 | 0.0294 |
| | N | 10 | 10 | 10 | 10 |

## Table 22 - Summary of Mean Hematology Differential Data: Toxicity Group Female Rats

| Sex: Female | | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
|---|---|---|---|---|---|
| Neutro (%) | Mean | 18.42 | 12.07 | 13.92 | 16.26 |
| | SD | 7.08 | 5.95 | 6.90 | 8.67 |
| | N | 9 | 9 | 9 | 10 |
| Abs Neut ($10^3$/uL) | Mean | 0.8704 | 0.6211 | 0.8207 | 0.9216 |
| | SD | 0.3336 | 0.2836 | 0.6115 | 0.6555 |
| | N | 9 | 9 | 9 | 10 |
| Lymph (%) | Mean | 70.68 | 78.77 | 75.94 | 72.98 |
| | SD | 8.18 | 6.13 | 7.56 | 9.41 |
| | N | 9 | 9 | 9 | 10 |
| Abs Lymph ($10^3$/uL) | Mean | 3.6156 | 4.3722 | 4.0878 | 4.0270 |
| | SD | 1.5931 | 1.5565 | 1.0612 | 0.9182 |
| | N | 9 | 9 | 9 | 10 |
| Mono *[1] (%) | Mean | 6.29 | 4.42 | 5.68 | 6.58 |
| | SD | 2.80 | 0.95 | 1.39 | 2.25 |
| | N | 9 | 9 | 9 | 10 |
| Abs Mono ($10^3$/uL) | Mean | 0.3229 | 0.2388 | 0.3100 | 0.3755 |
| | SD | 0.1747 | 0.0717 | 0.1139 | 0.1871 |
| | N | 9 | 9 | 9 | 10 |
| Eosin (%) | Mean | 3.26 | 3.36 | 2.90 | 2.79 |
| | SD | 0.86 | 1.50 | 0.98 | 1.04 |
| | N | 9 | 9 | 9 | 10 |
| Abs Eosin ($10^3$/uL) | Mean | 0.1632 | 0.1736 | 0.1517 | 0.1571 |
| | SD | 0.0698 | 0.0627 | 0.0519 | 0.0750 |
| | N | 9 | 9 | 9 | 10 |
| Baso (%) | Mean | 1.34 | 1.40 | 1.56 | 1.41 |
| | SD | 0.70 | 0.54 | 0.61 | 0.54 |
| | N | 9 | 9 | 9 | 10 |
| Abs Baso ($10^3$/uL) | Mean | 0.0659 | 0.0812 | 0.0883 | 0.0809 |
| | SD | 0.0335 | 0.0507 | 0.0481 | 0.0403 |
| | N | 9 | 9 | 9 | 10 |

[1]Group Factor 1 Way ANOVA: * - 5% significance level]

# Table 23 - Summary of Mean Prothrombin Time in Rats

| Sex: Male | | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
|---|---|---|---|---|---|
| Prothrombin *** Time (Seconds) | Mean | 14.13 | 14.06 | 14.81 | 15.86 *** |
| | SD | 0.49 | 0.42 | 1.10 | 1.36 |
| | N | 10 | 10 | 10 | 10 |

*[Group Factor 1 Way ANOVA: ** - 1% significance level]
*[* - 1% significance level]

## Table 23 - Summary of Mean Prothrombin Time in Rats Cont.

| Sex: Female | | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
|---|---|---|---|---|---|
| Prothrombin [**1] Time (Seconds) | Mean | 13.98 | 13.96 | 13.20 [**2] | 13.09 [**2] |
| | SD | 0.49 | 0.37 | 0.37 | 0.50 |
| | N | 9 | 9 | 9 | 10 |

[1]Group Factor 1 Way ANOVA: ** - 1% significance level]
[2]** - 1% significance level]

# Table 24 - Summary of Mean Clinical Chemistry Data: Male Rats

| Sex: Male | | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
|---|---|---|---|---|---|
| ALP **1 (U/L) | Mean | 140.7 | 133.3 | 100.0 **2 | 89.8 **2 |
| | SD | 43.2 | 27.1 | 21.6 | 20.9 |
| | N | 10 | 10 | 10 | 10 |
| ALT **1 (U/L) | Mean | 17.6 | 21.5 | 20.5 | 27.1 **2 |
| | SD | 3.4 | 3.7 | 3.5 | 8.4 |
| | N | 10 | 10 | 10 | 10 |
| AST **1 (U/L) | Mean | 85.5 | 70.8 *3 | 58.0 **2 | 48.8 **2 |
| | SD | 13.8 | 13.1 | 8.7 | 5.1 |
| | N | 10 | 10 | 10 | 10 |
| TBILI **1 (mg/dL) | Mean | 0.122 | 0.103 | 0.088 **2 | 0.084 **2 |
| | SD | 0.031 | 0.013 | 0.017 | 0.024 |
| | N | 10 | 10 | 10 | 10 |
| ALB *4 (g/dL) | Mean | 3.72 | 3.69 | 3.57 *3 | 3.62 |
| | SD | 0.16 | 0.11 | 0.07 | 0.11 |
| | N | 10 | 10 | 10 | 10 |
| TP *4 (g/dL) | Mean | 5.69 | 5.78 | 5.70 | 5.94 *3 |
| | SD | 0.22 | 0.19 | 0.25 | 0.14 |
| | N | 10 | 10 | 10 | 10 |
| BUN **1 (mg/dL) | Mean | 11.3 | 12.2 | 13.1 | 14.4 **2 |
| | SD | 1.3 | 1.9 | 2.0 | 2.1 |
| | N | 10 | 10 | 10 | 10 |
| CREAT (mg/dL) | Mean | 0.31 | 0.29 | 0.29 | 0.28 |
| | SD | 0.03 | 0.03 | 0.03 | 0.04 |
| | N | 10 | 10 | 10 | 10 |
| GLUC (mg/dL) | Mean | 136.6 | 138.8 | 141.8 | 143.5 |
| | SD | 8.8 | 15.8 | 19.9 | 9.3 |
| | N | 10 | 10 | 10 | 10 |
| CHOL (mg/dL) | Mean | 47.8 | 44.6 | 45.7 | 48.6 |
| | SD | 11.8 | 10.5 | 9.1 | 12.3 |
| | N | 10 | 10 | 10 | 10 |

*[Group Factor 1 Way ANOVA; ** - 1% significance level]

*[** - 1% significance level]

*[* - 5% significance level]

* [Group Factor 1 Way ANOVA; * - 5% significance level]

# Table 24 - Summary of Mean Clinical Chemistry Data: Male Rats

| Sex: Male | | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
|---|---|---|---|---|---|
| CA (mg/dL) | Mean | 9.78 | 9.85 | 9.85 | 10.00 |
| | SD | 0.34 | 0.28 | 0.23 | 0.27 |
| | N | 10 | 10 | 10 | 10 |
| PHOS (mg/dL) | Mean | 7.58 | 7.69 | 7.60 | 7.20 |
| | SD | 0.62 | 0.56 | 0.79 | 0.51 |
| | N | 10 | 10 | 10 | 10 |
| NA **[1] (mmol/L) | Mean | 141.4 | 140.8 | 140.8 | 139.8 **[2] |
| | SD | 0.8 | 1.1 | 0.6 | 0.9 |
| | N | 10 | 10 | 10 | 10 |
| K (mmol/L) | Mean | 4.50 | 4.43 | 4.49 | 4.43 |
| | SD | 0.22 | 0.22 | 0.25 | 0.25 |
| | N | 10 | 10 | 10 | 10 |
| CL (mmol/L) | Mean | 102.8 | 102.0 | 103.0 | 102.9 |
| | SD | 1.3 | 0.8 | 1.1 | 1.4 |
| | N | 10 | 10 | 10 | 10 |

[1][Group Factor 1 Way ANOVA: ** - 1% significance level]
[2][** - 1% significance level]

## Table 25 - Summary of Mean Clinical Chemistry Data: Toxicity Group Female Rats

| Sex: Female | | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
|---|---|---|---|---|---|
| ALP ** [1] (U/L) | Mean | 82.9 | 75.1 | 58.8 ** [2] | 48.3 ** [2] |
| | SD | 17.8 | 17.8 | 17.2 | 14.1 |
| | N | 9 | 9 | 10 | 10 |
| ALT ** [1] (U/L) | Mean | 19.2 | 19.7 | 22.0 | 26.9 ** [2] |
| | SD | 4.2 | 3.9 | 4.8 | 4.9 |
| | N | 9 | 9 | 10 | 10 |
| AST * [3] (U/L) | Mean | 60.7 | 76.0 * [4] | 68.1 | 59.3 |
| | SD | 7.7 | 9.6 | 12.8 | 15.1 |
| | N | 9 | 9 | 10 | 10 |
| TBILI ** [1] (mg/dL) | Mean | 0.124 | 0.132 | 0.092 ** [4] | 0.088 * [5] |
| | SD | 0.025 | 0.019 | 0.023 | 0.033 |
| | N | 9 | 9 | 10 | 10 |
| ALB (g/dL) | Mean | 4.06 | 4.16 | 4.06 | 3.86 |
| | SD | 0.18 | 0.22 | 0.34 | 0.23 |
| | N | 9 | 9 | 10 | 10 |
| TP * [3] (g/dL) | Mean | 6.02 | 5.88 | 6.03 | 6.37 |
| | SD | 0.26 | 0.41 | 0.33 | 0.25 |
| | N | 9 | 9 | 10 | 10 |
| BUN (mg/dL) | Mean | 13.2 | 13.3 | 14.2 | 15.7 |
| | SD | 2.8 | 2.3 | 2.5 | 2.1 |
| | N | 9 | 9 | 10 | 10 |
| CREAT (mg/dL) | Mean | 0.33 | 0.32 | 0.33 | 0.33 |
| | SD | 0.05 | 0.07 | 0.05 | 0.07 |
| | N | 9 | 9 | 10 | 10 |
| GLUC (mg/dL) | Mean | 135.7 | 127.4 | 124.4 | 124.8 |
| | SD | 12.7 | 14.2 | 15.7 | 9.6 |
| | N | 9 | 9 | 10 | 10 |
| CHOL ** [1] (mg/dL) | Mean | 56.3 | 57.1 | 62.5 | 85.7 ** [2] |
| | SD | 6.8 | 13.6 | 12.0 | 10.6 |
| | N | 9 | 9 | 10 | 10 |

[1] [Group Factor 1 Way ANOVA: ** - 1% significance level]

[2] [** - 1% significance level]

[3] [Group Factor 1 Way ANOVA: * - 5% significance level]

[4] [* - 5% significance level]

## Table 25 - Summary of Mean Clinical Chemistry Data: Toxicity Group Female Rats Cont.

| Sex: Female | | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
|---|---|---|---|---|---|
| CA (mg/dL) | Mean | 9.86 | 9.82 | 9.79 | 9.92 |
| | SD | 0.29 | 0.35 | 0.34 | 0.29 |
| | N | 9 | 9 | 10 | 10 |
| PHOS (mg/dL) | Mean | 7.01 | 7.03 | 6.61 | 6.37 |
| | SD | 0.72 | 0.58 | 0.50 | 0.59 |
| | N | 9 | 9 | 10 | 10 |
| NA (mmol/L) | Mean | 139.8 | 140.1 | 139.6 | 138.5 |
| | SD | 0.7 | 1.5 | 1.6 | 1.2 |
| | N | 9 | 9 | 10 | 10 |
| K (mmol/L) | Mean | 4.11 | 4.11 | 4.07 | 3.99 |
| | SD | 0.16 | 0.25 | 0.16 | 0.19 |
| | N | 9 | 9 | 10 | 10 |
| CL (mmol/L) | Mean | 104.1 | 103.8 | 103.5 | 102.8 |
| | SD | 1.5 | 1.4 | 1.0 | 1.4 |
| | N | 9 | 9 | 10 | 10 |

# Table 26 - Summary of Macroscopic Observations

| Removal Reasons: All of those SELECTED | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| ADRENAL GLANDS; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 9 | 7 | 10 | 10 | 9 | 10 | 8 |
| Discoloration; dark | (0) | (1) | (0) | (0) | (0) | (0) | (0) | (0) |
| mild | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Discoloration; red; unilateral; single | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Enlarged | (0) | (0) | (2) | (0) | (0) | (0) | (0) | (2) |
| minimal | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 |
| BONE MARROW, STERNUM; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| BRAIN; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| EPIDIDYMIDES; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (-) | (-) | (-) | (-) |
| No Visible Lesions | 10 | 10 | 10 | 10 | - | - | - | - |
| HEART; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| INTESTINE, CECUM; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| INTESTINE, COLON; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 9 | 8 | 10 | 8 | 10 | 9 |
| Dilation | 0 | 0 | 1 | 2 | 0 | 1 | 0 | 1 |
| INTESTINE, DUODENUM; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |

# Table 26 - Summary of Macroscopic Observations Cont.

| Removal Reasons: All of those SELECTED | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| INTESTINE, ILEUM; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| INTESTINE, JEJUNUM; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| KIDNEYS; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 9 | 10 | 9 | 10 | 10 |
| Discoloration; yellow; unilateral | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| LIVER; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 9 | 8 | 3 | 10 | 9 | 8 | 4 |
| Discoloration | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 |
| Discoloration; mottled | 0 | 1 | 2 | 6 | 0 | 0 | 1 | 1 |
| Enlarged | 0 | 0 | 0 | 1 | 0 | 0 | (1) | (4) |
| minimal | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 3 |
| LUNGS; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 9 | 8 | 6 | 10 | 9 | 10 | 9 |
| Discoloration; focal | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 |
| Discoloration; dark; multiple | 0 | 0 | 2 | 2 | 0 | 0 | 0 | 0 |
| Hemorrhage; red; single | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| LYMPH NODE, MEDIASTINAL; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| LYMPH NODE, MESENTERIC; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| NERVE, SCIATIC; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |

# Table 26 - Summary of Macroscopic Observations Cont.

| Removal Reasons: All of those SELECTED | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| NERVE, SCIATIC; (continued) | | | | | | | | |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| OVARIES; | | | | | | | | |
| Submitted | (-) | (-) | (-) | (-) | (10) | (9) | (10) | (10) |
| No Visible Lesions | - | - | - | - | 10 | 8 | 10 | 10 |
| Enlarged | (-) | (-) | (-) | (-) | (0) | (1) | (0) | (0) |
| minimal | - | - | - | - | 0 | 1 | 0 | 0 |
| PROSTATE GLAND; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (-) | (-) | (-) | (-) |
| No Visible Lesions | 10 | 10 | 10 | 10 | - | - | - | - |
| SEMINAL VESICLES; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (-) | (-) | (-) | (-) |
| No Visible Lesions | 10 | 9 | 10 | 8 | - | - | - | - |
| Small | (0) | (1) | (0) | 1 | (-) | (-) | (-) | (-) |
| minimal | 0 | 1 | 0 | 0 | - | - | - | - |
| Enlarged | (0) | (0) | (0) | (1) | (-) | (-) | (-) | (-) |
| minimal | 0 | 0 | 0 | 1 | - | - | - | - |
| SPINAL CORD; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| SPLEEN; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 9 | 10 | 10 | 8 | 9 | 10 |
| Discoloration; dark | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Enlarged | (0) | (0) | (1) | (0) | (0) | (0) | (1) | (0) |
| minimal | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 |
| STOMACH; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| TESTES; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (-) | (-) | (-) | (-) |

# Table 26 - Summary of Macroscopic Observations Cont.

| Removal Reasons: All of those SELECTED | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| TESTES; (continued) | | | | | | | | |
| No Visible Lesions | 10 | 10 | 10 | 9 | - | - | - | - |
| Discoloration; hemorrhagic; unilateral | 0 | 0 | 0 | 1 | - | - | - | - |
| THYMUS; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 9 | 10 | 6 | 5 | 10 | 7 | 10 | 10 |
| Discoloration | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Discoloration; few | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Discoloration; dark; multiple | (0) | (0) | (0) | (1) | (0) | (0) | (0) | (0) |
| minimal | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Discoloration; red; unilateral; multifocal | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Discoloration; red; multifocal | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Discoloration; red; multiple | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Enlarged | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 |
| Small | 0 | 0 | 3 | (4) | 0 | 0 | 0 | 0 |
| minimal | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| THYROID GLANDS; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| TRACHEA; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| URINARY BLADDER; | | | | | | | | |
| Submitted | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| No Visible Lesions | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| UTERUS; | | | | | | | | |
| Submitted | (-) | (-) | (-) | (-) | (10) | (9) | (10) | (10) |
| No Visible Lesions | - | - | - | - | 10 | 9 | 10 | 10 |

## Table 27 - Summary of Mean Organ Weights (grams) and Organ Weight to Body Weight Ratios: Male Rats

| | | MALES | | | |
|---|---|---|---|---|---|
| | | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| Terminal Bodyweight ..... | Mean (g) | 430.83 | 421.51 | 420.22 | 401.20 |
| | S.D. | 24.54 | 31.96 | 25.11 | 26.61 |
| | N | 10 | 10 | 10 | 10 |
| ADRENAL GLANDS ..... | Mean (g) | 0.05935** | 0.05482 | 0.05601 | 0.04514** |
| | S.D. | 0.01020 | 0.00472 | 0.00777 | 0.00641 |
| | N | 10 | 10 | 10 | 10 |
| | Mean (%) | 0.01* | 0.01 | 0.01 | 0.01* |
| | S.D. | 0.00 | 0.00 | 0.00 | 0.00 |
| | N | 10 | 10 | 10 | 10 |
| BRAIN ..... | Mean (g) | 1.9946 | 1.9745 | 1.9905 | 1.9680 |
| | S.D. | 0.0772 | 0.0802 | 0.1014 | 0.0868 |
| | N | 10 | 10 | 10 | 10 |
| | Mean (%) | 0.46 | 0.47 | 0.48 | 0.49 |
| | S.D. | 0.04 | 0.03 | 0.03 | 0.03 |
| | N | 10 | 10 | 10 | 10 |
| EPIDIDYMIDES ..... | Mean (g) | 1.2160 | 1.1929 | 1.1653 | 1.1224 |
| | S.D. | 0.0977 | 0.0939 | 0.0553 | 0.0741 |
| | N | 10 | 10 | 10 | 10 |
| | Mean (%) | 0.28 | 0.28 | 0.28 | 0.28 |
| | S.D. | 0.03 | 0.03 | 0.02 | 0.02 |
| | N | 10 | 10 | 10 | 10 |
| HEART ..... | Mean (g) | 1.3634 | 1.2869 | 1.3432 | 1.2535 |
| | S.D. | 0.1150 | 0.0869 | 0.1509 | 0.1306 |
| | N | 10 | 10 | 10 | 10 |
| | Mean (%) | 0.32 | 0.31 | 0.32 | 0.31 |
| | S.D. | 0.02 | 0.02 | 0.03 | 0.02 |
| | N | 10 | 10 | 10 | 10 |

Statistics Test: 1 Way Analysis of Variance: * - 5% significance level; ** - 1% significance level

## Table 27 - Summary of Mean Organ Weights (grams) and Organ Weight to Body Weight Ratios: Male Rats Cont.

| | | MALES | | | |
|---|---|---|---|---|---|
| | | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| KIDNEYS | Mean (g) | 2.8417 | 2.8572 | 3.0299 | 2.8508 |
| | S.D. | 0.1411 | 0.2409 | 0.3713 | 0.2185 |
| | N | 10 | 10 | 10 | 10 |
| | Mean (%) | 0.66* | 0.68 | 0.72* | 0.71 |
| | S.D. | 0.04 | 0.05 | 0.07 | 0.04 |
| | N | 10 | 10 | 10 | 10 |
| LIVER | Mean (g) | 12.4102** | 12.7829 | 14.8119** | 16.2321** |
| | S.D. | 1.1407 | 1.2421 | 1.9477 | 1.3452 |
| | N | 10 | 10 | 10 | 10 |
| | Mean (%) | 2.88** | 3.03 | 3.51** | 4.05** |
| | S.D. | 0.17 | 0.12 | 0.30 | 0.34 |
| | N | 10 | 10 | 10 | 10 |
| PROSTATE GLAND | Mean (g) | 0.8422 | 0.8371 | 0.8244 | 0.7347 |
| | S.D. | 0.0970 | 0.1668 | 0.1496 | 0.1729 |
| | N | 10 | 10 | 10 | 10 |
| | Mean (%) | 0.20 | 0.20 | 0.20 | 0.18 |
| | S.D. | 0.02 | 0.03 | 0.04 | 0.03 |
| | N | 10 | 10 | 10 | 10 |
| SEMINAL VESICLES | Mean (g) | 1.8543 | 1.5639 | 1.7048 | 1.7136 |
| | S.D. | 0.2488 | 0.3664 | 0.2918 | 0.4991 |
| | N | 10 | 10 | 10 | 10 |
| | Mean (%) | 0.43 | 0.37 | 0.41 | 0.42 |
| | S.D. | 0.06 | 0.08 | 0.07 | 0.11 |
| | N | 10 | 10 | 10 | 10 |
| SPLEEN | Mean (g) | 0.7276 | 0.7246 | 0.7321 | 0.6381 |
| | S.D. | 0.1023 | 0.0709 | 0.0868 | 0.1081 |
| | N | 10 | 10 | 10 | 10 |
| | Mean (%) | 0.17 | 0.17 | 0.17 | 0.16 |
| | S.D. | 0.02 | 0.02 | 0.02 | 0.02 |
| | N | 10 | 10 | 10 | 10 |

Statistics Test: 1 Way Analysis of Variance: * - 5% significance level; ** - 1% significance level

## Table 27 - Summary of Mean Organ Weights (grams) and Organ Weight to Body Weight Ratios: Male Rats Cont.

| | | MALES | | | |
|---|---|---|---|---|---|
| | | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| TESTES ..... | Mean (g) | 3.4618** | 3.5100 | 3.3643 | 3.0551** |
| | S.D. | 0.2063 | 0.2376 | 0.2488 | 0.2743 |
| | N | 10 | 10 | 10 | 10 |
| | Mean (%) | 0.81 | 0.84 | 0.80 | 0.76 |
| | S.D. | 0.08 | 0.09 | 0.09 | 0.08 |
| | N | 10 | 10 | 10 | 10 |
| THYMUS ..... | Mean (g) | 0.4265** | 0.4256 | 0.3509 | 0.2935** |
| | S.D. | 0.1060 | 0.0789 | 0.0855 | 0.0806 |
| | N | 10 | 10 | 10 | 10 |
| | Mean (%) | 0.10* | 0.10 | 0.08 | 0.07* |
| | S.D. | 0.02 | 0.02 | 0.02 | 0.02 |
| | N | 10 | 10 | 10 | 10 |

Statistics Test: 1 Way Analysis of Variance: * - 5% significance level; ** - 1% significance level

## Table 28 - Summary of Mean Organ Weights (grams) and Organ Weight to Body Weight Ratios: Toxicity Group Female Rats

| | | FEMALES | | | |
|---|---|---|---|---|---|
| | | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| Terminal Bodyweight ..... | Mean (g) | 259.56 | 256.32 | 257.99 | 254.47 |
| | S.D. | 24.11 | 21.74 | 16.58 | 21.50 |
| | N | 10 | 9 | 10 | 10 |
| ADRENAL GLANDS ..... | Mean (g) | 0.07083 | 0.06791 | 0.07163 | 0.06826 |
| | S.D. | 0.01562 | 0.00845 | 0.00758 | 0.01202 |
| | N | 10 | 9 | 10 | 10 |
| | Mean (%) | 0.03 | 0.03 | 0.03 | 0.03 |
| | S.D. | 0.01 | 0.00 | 0.00 | 0.00 |
| | N | 10 | 9 | 10 | 10 |
| BRAIN ..... | Mean (g) | 1.9317 | 1.9184 | 1.9040 | 1.9163 |
| | S.D. | 0.1415 | 0.0555 | 0.0602 | 0.0667 |
| | N | 10 | 9 | 10 | 10 |
| | Mean (%) | 0.75 | 0.75 | 0.74 | 0.76 |
| | S.D. | 0.06 | 0.05 | 0.04 | 0.06 |
| | N | 10 | 9 | 10 | 10 |
| HEART ..... | Mean (g) | 0.8813 | 0.8482 | 0.8638 | 0.8740 |
| | S.D. | 0.0950 | 0.0802 | 0.0612 | 0.0620 |
| | N | 10 | 9 | 10 | 10 |
| | Mean (%) | 0.34 | 0.33 | 0.33 | 0.34 |
| | S.D. | 0.02 | 0.02 | 0.01 | 0.02 |
| | N | 10 | 9 | 10 | 10 |
| KIDNEYS ..... | Mean (g) | 1.7638 | 1.7883 | 1.8017 | 1.7405 |
| | S.D. | 0.1797 | 0.1541 | 0.1928 | 0.1165 |
| | N | 10 | 9 | 10 | 10 |
| | Mean (%) | 0.68 | 0.70 | 0.70 | 0.69 |
| | S.D. | 0.06 | 0.04 | 0.04 | 0.03 |
| | N | 10 | 9 | 10 | 10 |

Statistics Test: 1 Way Analysis of Variance: * - 5% significance level; ** - 1% significance level

## Table 28 - Summary of Mean Organ Weights (grams) and Organ Weight to Body Weight Ratios: Toxicity Group Female Rats Cont.

| | | FEMALES | | | |
|---|---|---|---|---|---|
| | | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| LIVER | Mean (g) | 7.4828** | 7.4317 | 9.2845** | 12.0684** |
| | S.D. | 0.9933 | 0.7038 | 1.0454 | 1.4528 |
| | N | 10 | 9 | 10 | 10 |
| | Mean (%) | 2.88** | 2.90 | 3.59** | 4.74** |
| | S.D. | 0.19 | 0.19 | 0.22 | 0.39 |
| | N | 10 | 9 | 10 | 10 |
| OVARIES | Mean (g) | 0.13319 | 0.13484 | 0.12877 | 0.14244 |
| | S.D. | 0.02395 | 0.02187 | 0.01578 | 0.02040 |
| | N | 10 | 9 | 10 | 10 |
| | Mean (%) | 0.05 | 0.05 | 0.05 | 0.06 |
| | S.D. | 0.01 | 0.01 | 0.01 | 0.01 |
| | N | 10 | 9 | 10 | 10 |
| SPLEEN | Mean (g) | 0.5359 | 0.5747 | 0.5324 | 0.5246 |
| | S.D. | 0.1114 | 0.0774 | 0.0935 | 0.1287 |
| | N | 10 | 9 | 10 | 10 |
| | Mean (%) | 0.21 | 0.22 | 0.21 | 0.20 |
| | S.D. | 0.03 | 0.02 | 0.03 | 0.04 |
| | N | 10 | 9 | 10 | 10 |
| THYMUS | Mean (g) | 0.4163 | 0.4402 | 0.3713 | 0.3330 |
| | S.D. | 0.1198 | 0.1450 | 0.0629 | 0.0591 |
| | N | 10 | 9 | 10 | 10 |
| | Mean (%) | 0.16* | 0.17 | 0.14 | 0.13 |
| | S.D. | 0.04 | 0.05 | 0.02 | 0.02 |
| | N | 10 | 9 | 10 | 10 |
| UTERUS | Mean (g) | 0.5106 | 0.5123 | 0.7248 | 0.4953 |
| | S.D. | 0.1859 | 0.0592 | 0.4374 | 0.1276 |
| | N | 10 | 9 | 10 | 10 |
| | Mean (%) | 0.20 | 0.20 | 0.28 | 0.19 |
| | S.D. | 0.07 | 0.02 | 0.18 | 0.04 |
| | N | 10 | 9 | 10 | 10 |

Statistics Test: 1 Way Analysis of Variance: * - 5% significance level; ** - 1% significance level

## Table 29 - Summary of Histopathology Findings: Male Rats

| Sex: Male | | 0 mg/kg/day | 50 mg/kg/day | 250 mg/kg/day | 500 mg/kg/day |
|---|---|---|---|---|---|
| EPIDIDYMIDES; Immature; spermatid | # Examined | 10 | 0 | 0 | 10 |
| | All Grades | 0 | 0 | 0 | 1 |
| | Minimal | 0 | 0 | 0 | 1 |
| HEART; Inflammation; chronic; focal | # Examined | 10 | 0 | 0 | 10 |
| | All Grades | 1 | 0 | 0 | 1 |
| | Minimal | 1 | 0 | 0 | 1 |
| KIDNEYS; Hyperplasia; tubular; focal | # Examined | 10 | 0 | 0 | 10 |
| | All Grades | 0 | 0 | 0 | 1 |
| | Moderate | 0 | 0 | 0 | 1 |
| KIDNEYS; Infarction; focal | # Examined | 10 | 0 | 0 | 10 |
| | All Grades | 0 | 0 | 0 | 1 |
| | Moderate | 0 | 0 | 0 | 1 |
| KIDNEYS; Inflammation; chronic; focal | # Examined | 10 | 0 | 0 | 10 |
| | All Grades | 3 | 0 | 0 | 1 |
| | Mild | 3 | 0 | 0 | 1 |
| KIDNEYS; Basophilia; tubular; focal | # Examined | 10 | 0 | 0 | 10 |
| | All Grades | 4 | 0 | 0 | 5 |
| | Minimal | 3 | 0 | 0 | 4 |
| | Mild | 1 | 0 | 0 | 1 |
| LIVER; Hypertrophy; centrilobular | # Examined | 10 | 10 | 10 | 10 |
| | All Grades | 0 +++ | 1 | 8 +++ | 8 +++ |
| | Minimal | 0 | 1 | 7 | 3 |
| | Mild | 0 | 0 | 1 | 5 |
| LIVER; Inflammation; chronic; multifocal | # Examined | 10 | 10 | 10 | 10 |
| | All Grades | 9 | 8 | 8 | 1 |
| | Minimal | 8 | 7 | 8 | 1 |
| | Mild | 1 | 1 | 0 | 0 |
| LIVER; Inflammation; chronic; periportal | # Examined | 10 | 10 | 10 | 10 |
| | All Grades | 0 +++ | 0 | 0 | 9 +++ |
| | Minimal | 0 | 0 | 0 | 4 |
| | Mild | 0 | 0 | 0 | 5 |

Plus Signs indicate a significant trend by the Cochran-Armitage Test across treatment groups (in the control column) or between control and a treatment group by Fisher's Exact Test with p-values of + < 0.05, ++ < 0.02 or +++ < 0.01. Asterisks indicate a significant shift in grade across treatment groups (in the control column) with p-values of * < 0.05, ** < 0.02 or *** < 0.01.

## Table 29 - Summary of Histopathology Findings: Male Rats Cont.

| Sex: Male | | 0 mg/kg/day | 50 mg/kg/day | 250 mg/kg/day | 500 mg/kg/day |
|---|---|---|---|---|---|
| LIVER; Hyperplasia, Bile Duct, Associated with Protoporphyrinosis | # Examined | 10 | 10 | 10 | 10 |
| | All Grades | 0 +++ | 0 | 0 | 8 +++ |
| | Minimal | 0 | 0 | 0 | 3 |
| | Mild | 0 | 0 | 0 | 3 |
| | Moderate | 0 | 0 | 0 | 2 |
| LIVER; Vacuolation; hepatocellular; centrilobular | # Examined | 10 | 10 | 10 | 10 |
| | All Grades | 0 | 1 | 0 | 0 |
| | Mild | 0 | 1 | 0 | 0 |
| LIVER; Vacuolation; hepatocellular; periportal | # Examined | 10 | 10 | 10 | 10 |
| | All Grades | 2 | 0 | 2 | 3 |
| | Minimal | 1 | 0 | 1 | 0 |
| | Mild | 1 | 0 | 1 | 3 |
| LIVER; Protoporphyrinosis | # Examined | 10 | 10 | 10 | 10 |
| | All Grades | 0 +++ | 0 | 0 | 9 +++ |
| | Minimal | 0 | 0 | 0 | 5 |
| | Mild | 0 | 0 | 0 | 1 |
| | Moderate | 0 | 0 | 0 | 3 |
| LUNGS; Hemorrhage; focal | # Examined | 10 | 10 | 10 | 10 |
| | All Grades | 2 | 0 | 1 | 1 |
| | Minimal | 2 | 0 | 1 | 1 |
| LUNGS; Hyperplasia; lymphoid tissue | # Examined | 10 | 10 | 10 | 10 |
| | All Grades | 0 | 1 | 1 | 0 |
| | Mild | 0 | 1 | 1 | 0 |
| LUNGS; Inflammation; acute; focal | # Examined | 10 | 10 | 10 | 10 |
| | All Grades | 1 | 0 | 0 | 0 |
| | Minimal | 1 | 0 | 0 | 0 |
| LUNGS; Inflammation; chronic; focal | # Examined | 10 | 10 | 10 | 10 |
| | All Grades | 1 | 0 | 0 | 0 |
| | Minimal | 1 | 0 | 0 | 0 |
| LUNGS; Inflammation; chronic; multifocal | # Examined | 10 | 10 | 10 | 10 |
| | All Grades | 1 | 0 | 0 | 1 |
| | Minimal | 1 | 0 | 0 | 1 |

Plus Signs indicate a significant trend by the Cochran-ArmitageTest across treatment groups (in the control column) or between control and a treatment group by Fisher's Exact Test with p-values of + < 0.05, ++ < 0.02 or +++ < 0.01. Asterisks indicate a significant shift in grade across treatment groups (in the control column) with p-values of * < 0.05, ** < 0.02 or *** < 0.01.

## Table 29 - Summary of Histopathology Findings: Male Rats Cont.

| Sex: Male | | 0 mg/kg/day | 50 mg/kg/day | 250 mg/kg/day | 500 mg/kg/day |
|---|---|---|---|---|---|
| LUNGS; Histocytosis | # Examined | 10 | 10 | 10 | 10 |
| | All Grades | 4 ++* | 4 | 8 | 8 |
| | Minimal | 4 | 4 | 4 | 8 |
| | Mild | 0 | 0 | 4 | 0 |
| PROSTATE GLAND; Inflammation; chronic | # Examined | 10 | 10 | 10 | 10 |
| | All Grades | 2 +* | 6 | 5 | 7 + |
| | Minimal | 0 | 3 | 5 | 1 |
| | Mild | 1 | 2 | 0 | 6 |
| | Moderate | 1 | 1 | 0 | 0 |
| PROSTATE GLAND; Inflammation; chronic-active | # Examined | 10 | 10 | 10 | 10 |
| | All Grades | 0 | 1 | 0 | 0 |
| | Marked | 0 | 1 | 0 | 0 |
| PROSTATE GLAND; Necrosis; single cell | # Examined | 10 | 10 | 10 | 10 |
| | All Grades | 1 | 0 | 0 | 1 |
| | Minimal | 1 | 0 | 0 | 1 |
| SEMINAL VESICLES; Atrophy; unilateral | # Examined | 10 | 0 | 0 | 10 |
| | All Grades | 0 | 0 | 0 | 1 |
| | Mild | 0 | 0 | 0 | 1 |
| TESTES; Degeneration; spermatid | # Examined | 10 | 0 | 0 | 10 |
| | All Grades | 0 | 0 | 0 | 1 |
| | Minimal | 0 | 0 | 0 | 1 |
| TESTES; Cyst; seminiferous tubule | # Examined | 10 | 0 | 0 | 10 |
| | Present | 0 | 0 | 0 | 1 |
| THYROID GLANDS; Cyst; ultimobranchial | # Examined | 10 | 10 | 10 | 10 |
| | Present | 2 | 3 | 0 | 1 |
| THYROID GLANDS; Ectopic Thymus | # Examined | 10 | 10 | 10 | 10 |
| | Present | 1 | 0 | 0 | 0 |
| THYROID GLANDS; Hypertrophy; follicular | # Examined | 10 | 10 | 10 | 10 |
| | All Grades | 1 +++* | 0 | 8 +++ | 9 +++ |
| | Minimal | 1 | 0 | 5 | 1 |
| | Mild | 0 | 0 | 3 | 8 |

Plus Signs indicate a significant trend by the Cochran-Armitage Test across treatment groups (in the control column) or between control and a treatment group by Fisher's Exact Test with p-values of + < 0.05, ++ < 0.02 or +++ < 0.01. Asterisks indicate a significant shift in grade across treatment groups (in the control column) with p-values of * < 0.05, ** < 0.02 or *** < 0.01.

## Table 30 - Summary of Histopathological Findings: Toxicity Group Female Rats

| Sex: Female | | 0 mg/kg/day | 50 mg/kg/day | 250 mg/kg/day | 500 mg/kg/day |
|---|---|---|---|---|---|
| HEART; Hyperplasia; atrium; endocardium | # Examined | 10 | 0 | 0 | 10 |
| | All Grades | 0 | 0 | 0 | 1 |
| | Mild | 0 | 0 | 0 | 1 |
| KIDNEYS; Inflammation; chronic; focal | # Examined | 10 | 0 | 0 | 10 |
| | All Grades | 3 | 0 | 0 | 1 |
| | Minimal | 3 | 0 | 0 | 1 |
| KIDNEYS; Basophilia; tubular; focal | # Examined | 10 | 0 | 0 | 10 |
| | All Grades | 3 | 0 | 0 | 2 |
| | Minimal | 3 | 0 | 0 | 2 |
| LIVER; Hypertrophy; centrilobular | # Examined | 10 | 9 | 10 | 10 |
| | All Grades | 0 +++ | 0 | 8 +++ | 10 +++ |
| | Minimal | 0 | 0 | 4 | 0 |
| | Mild | 0 | 0 | 4 | 10 |
| LIVER; Inflammation; chronic; multifocal | # Examined | 10 | 9 | 10 | 10 |
| | All Grades | 7 | 9 | 6 | 4 |
| | Minimal | 6 | 9 | 4 | 4 |
| | Mild | 1 | 0 | 2 | 0 |
| LIVER; Vacuolation; hepatocellular; periportal | # Examined | 10 | 9 | 10 | 10 |
| | All Grades | 5 +++*** | 4 | 7 | 10 ++ |
| | Minimal | 3 | 4 | 2 | 0 |
| | Mild | 2 | 0 | 3 | 6 |
| | Moderate | 0 | 0 | 2 | 4 |
| LUNGS; Hemorrhage; focal | # Examined | 10 | 9 | 10 | 10 |
| | All Grades | 0 | 1 | 0 | 0 |
| | Minimal | 0 | 1 | 0 | 0 |
| LUNGS; Hyperplasia; lymphoid tissue | # Examined | 10 | 9 | 10 | 10 |
| | All Grades | 0 | 1 | 1 | 0 |
| | Mild | 0 | 1 | 1 | 0 |
| LUNGS; Inflammation; acute; focal | # Examined | 10 | 9 | 10 | 10 |
| | All Grades | 0 | 1 | 0 | 0 |
| | Minimal | 0 | 1 | 0 | 0 |

Plus Signs indicate a significant trend by the Cochran-Armitage Test across treatment groups (in the control column) or between control and a treatment group by Fisher's Exact Test with p-values of + < 0.05, ++ < 0.02 or +++ < 0.01. Asterisks indicate a significant shift in grade across treatment groups (in the control column) with p-values of * < 0.05, ** < 0.02 or *** < 0.01.

## Table 30 - Summary of Histopathological Findings: Toxicity Group Female Rats

| Sex: Female | | 0 mg/kg/day | 50 mg/kg/day | 250 mg/kg/day | 500 mg/kg/day |
|---|---|---|---|---|---|
| LUNGS; Inflammation; chronic; focal | # Examined | 10 | 9 | 10 | 10 |
| | All Grades | 0 | 0 | 1 | 0 |
| | Minimal | 0 | 0 | 1 | 0 |
| LUNGS; Histocytosis | # Examined | 10 | 9 | 10 | 10 |
| | All Grades | 3 | 3 | 2 | 5 |
| | Minimal | 3 | 3 | 1 | 5 |
| | Mild | 0 | 0 | 1 | 0 |
| OVARIES; Cyst; corpus luteum | # Examined | 10 | 0 | 0 | 10 |
| | Present | 1 | 0 | 0 | 1 |
| THYROID GLANDS; Cyst; ultimobranchial | # Examined | 10 | 0 | 0 | 10 |
| | Present | 2 | 0 | 0 | 3 |
| THYROID GLANDS; Ectopic Thymus | # Examined | 10 | 0 | 0 | 10 |
| | Present | 1 | 0 | 0 | 0 |
| THYROID GLANDS; Hypertrophy; follicular | # Examined | 10 | 0 | 0 | 10 |
| | All Grades | 0 | 0 | 0 | 1 |
| | Minimal | 0 | 0 | 0 | 1 |
| URINARY BLADDER; Inflammation; chronic; focal | # Examined | 10 | 0 | 0 | 10 |
| | All Grades | 0 | 0 | 0 | 1 |
| | Minimal | 0 | 0 | 0 | 1 |
| UTERUS; Inflammation; acute; diffuse | # Examined | 10 | 0 | 0 | 10 |
| | All Grades | 1 | 0 | 0 | 0 |
| | Mild | 1 | 0 | 0 | 0 |

Plus Signs indicate a significant trend by the Cochran-Armitage Test across treatment groups (in the control column) or between control and a treatment group by Fisher's Exact Test with p-values of + < 0.05, ++ < 0.02 or +++ < 0.01. Asterisks indicate a significant shift in grade across treatment groups (in the control column) with p-values of * < 0.05, ** < 0.02 or *** < 0.01.

## Table 31 - Summary of Mean Reproductive Parameters for Reproductive Group Female Rats

| Sex: Female | | Litter | | | | | | | Initial | | Final | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Days Gestation | Male Pups | Female Pups | Males/Females | Total Pups | Day 4 Viable Pups | Viable/Total | Litter Weight (Grams) | Average Pup Weight (Grams) | Litter Weight (Grams) | Average Pup Weight (Grams) | Total Implants | Corpora Lutea Counts | Post Partum Implantation loss (%) | Post Natal Implantation loss (%) |
| 0 mg/kg/day | Mean | 22 | 9 | 7 | 1.2 | 16 | 15 *** | 0.95 ** | 101.6 | 6.7 | 168.5 | 11.4 | 17 * | 24 | 9.4 | 1.2 |
| | SD | 0.6 | 2 | 1 | 0.3 | 2 | 3 | 0.11 | 17.0 | 0.4 | 25.8 | 1.6 | 1 | 6 | 14.0 | 3.7 |
| | N^ | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| 50 mg/kg/day | Mean | 22 | 8 | 7 | 1.2 | 15 | 15 | 0.98 | 102.5 | 6.8 | 163.1 | 10.9 | 16 | 22 | 7.5 | 1.4 |
| | SD | 0.3 | 2 | 2 | 0.5 | 2 | 2 | 0.03 | 12.6 | 0.2 | 17.9 | 0.8 | 2 | 5 | 6.0 | 2.7 |
| | N^ | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| 250 mg/kg/day | Mean | 22 | 8 | 7 | 1.4 | 15 | 15 | 0.98 | 104.8 | 7.0 | 163.3 | 11.0 | 17 | 21 | 10.3 | 0.7 |
| | SD | 0.5 | 2 | 2 | 1.1 | 2 | 2 | 0.03 | 15.3 | 0.3 | 22.3 | 0.9 | 2 | 4 | 3.6 | 2.2 |
| | N^ | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| 500 mg/kg/day | Mean | 23 | 6 | 7 | 0.9 | 13 | 12 | 0.94 | 89.5 | 7.2 | 125.3 | 10.7 | 15 | 21 | 19.2 | 4.6 |
| | SD | 0.0 | 3 | 4 | 0.5 | 5 | 5 | 0.08 | 29.8 | 0.8 | 42.3 | 2.3 | 3 | 5 | 20.8 | 7.9 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Litter Size Signficance | | | *** | *** | | | *** | * | *** | * | *** | *** | *** | | | |

^Data of non-pregnant female(s) with positive evidence of mating not included in calculations.

Note: Asterisks next to the control column indicate a significant treatment effect in the ANCOVA, asterisks in the litter size significance row indicate a significant litter effect in the ANCOVA.
p-values of * <0.05, * *<0.02 or *** <0.01.

## Table 32 - Summary of Reproductive Performance for Reproductive Group Female Rats

| | Group 1<br>0 mg/kg/day | Group 2<br>50 mg/kg/day | Group 3<br>250 mg/kg/day | Group 4<br>500 mg/kg/day |
|---|---|---|---|---|
| Females on Study | 10 | 10 | 10 | 10 |
| Females that died during study | 0 | 0 | 0 | 0 |
| Females euthanized in extremis | 0 | 0 | 0 | 0 |
| Females Allowed to Deliver | 10 | 10 | 10 | 10 |
| Nongravid | 1 | 1 | 1 | 0 |
| Gravid | 9 | 9 | 9 | 10 |
| Females with Evidence of Copulation | 10 | 10 | 10 | 10 |
| Number which delivered | 9 | 9 | 9 | 10 |
| Number which did not deliver | 1 | 1 | 1 | 0 |
| Females with No Evidence of Copulation | 0 | 0 | 0 | 0 |
| Number which delivered | 0 | 0 | 0 | 0 |
| Number which did not deliver | 0 | 0 | 0 | 0 |

## Table 33 - Protocol Deviations

| Protocol Section | Protocol Requirement | Deviation | Impact |
|---|---|---|---|
| 6 | A reserve sample will be retained.. | Stability of dimethylsilanediol has been demonstrated for only 66 days when stored at -65°C in the presence of desiccants. | None |
| 13.4 | N=10 in each group. | N=9 in toxicology female group 2 since an animal in the group 2 reproductive group was euthanized (gavage error) and one animals from group 2 toxicology females was transferred to the reproductive group. | None |
| 13.3 | Storage of dose suspensions will be 5+/-4 ° C. | There were excursions to greater than 9 degrees while the data logger was equilibrating and excursions below 1 degree. | None |
| 13.5 | Feedcr weights will be weighed on day 1 and new feeders will be weighed on day 8. | Feed inadvertently added to all but three control males and all control toxicity females on day 5 of study. | Yes |

# Appendix A: Individual Clinical Observations – Male Rats

Day numbers relative to Start Date

| Group | Sex | Animal | Clinical Sign | Site | -3 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | m | 5484 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5485 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5486 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5487 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5488 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5489 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5490 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . | X | X | X | X | X | X | X | X | X | X | X |
| | | | Soiling | Muzzle, General | . | . | . | . | . | . | . | . | . | . | C | . | . | . | . | . | . | . | . | . | . | . |
| | | 5491 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5492 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5493 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

Severity Codes: X = Present; D = Decreased; F = Focal; S = Small; C = Clear; R = Red;
Y = Yellow; W = Wet; M = Minimal (10-30%); M = Moderate (31-60%);

Group 1 - 0mg/kg Group 2 - 50mg/kg Group 3 - 250mg/kg Group 4 - 500mg/kg

# Appendix A: Individual Clinical Observations – Male Rats

| | | | | | Day numbers relative to Start Date | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Group | Sex | Animal | Clinical Sign | Site | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 |
| 1 | m | 5484 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X |
| | | 5485 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X |
| | | 5486 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X |
| | | 5487 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X |
| | | 5488 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X |
| | | 5489 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X |
| | | 5490 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X |
| | | | Soiling | Muzzle, General | . | . | . | . | . | . | . | . | . |
| | | 5491 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X |
| | | 5492 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X |
| | | 5493 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X |

Severity Codes: X = Present; D = Decreased; F = Focal; S = Small; C = Clear; R = Red;
Y = Yellow; W = Wet; M = Minimal (10-30%); M = Moderate (31-60%);

Group 1 - 0mg/kg Group 2 - 50mg/kg Group 3 - 250mg/kg Group 4 - 500mg/kg

# Appendix A: Individual Clinical Observations – Male Rats

Day numbers relative to Start Date

| Group | Sex | Animal | Clinical Sign | Site | -3 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | ■ | 5514 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5515 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5516 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5517 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5518 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5519 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5520 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5521 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5522 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5523 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

Severity Codes: X = Present; D = Decreased; F = Focal; S = Small; C = Clear; R = Red;
Y = Yellow; W = Wet; M = Minimal (10-30%); M = Moderate (31-60%);

Group 1 - 0mg/kg Group 2 - 50mg/kg Group 3 - 250mg/kg Group 4 - 500mg/kg

# Appendix A: Individual Clinical Observations – Male Rats

| Group | Sex | Animal | Clinical Sign | Site | Day numbers relative to Start Date 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | m | 5514 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X |
| | | 5515 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X |
| | | 5516 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X |
| | | 5517 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X |
| | | 5518 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X |
| | | 5519 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X |
| | | 5520 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X |
| | | 5521 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X |
| | | 5522 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X |
| | | 5523 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X |

Severity Codes: X = Present; D = Decreased; F = Focal; S = Small; C = Clear; R = Red;
Y = Yellow; W = Wet; M = Minimal (10-30%); M = Moderate (31-60%);

Group 1 - 0mg/kg Group 2 - 50mg/kg Group 3 - 250mg/kg Group 4 - 500mg/kg

# Appendix A: Individual Clinical Observations – Male Rats

Day numbers relative to Start Date

| Group | Sex | Animal | Clinical Sign | Site | -3 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | m | 5544 | No Abnormalities Detected | | X | X | . | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | | Soiling | Urogenital, General | . | . | Y | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | 5545 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | | Skin, Excessive Hair Loss | | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | 5546 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | X | . | . | . | X |
| | | | Soiling | Abdomen, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | Y | . | . | . | . | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | Y | Y | Y | . |
| | | 5547 | No Abnormalities Detected | | X | X | X | X | . | . | . | . | . | . | X | X | X | X | X | . | X | X | X | X | X | X |
| | | | Skin, Scab | Upper Back (Thoracic) | . | . | . | . | F | F | F | F | F | F | . | . | . | . | . | . | . | . | . | . | . | . |
| | | | Soiling | Muzzle, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | C | . | . | . | . | . | . |
| | | 5548 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5549 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | X |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | Y | . |
| | | 5550 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | . | . | X | X | X | X | X | X | . | . | X | X | X |
| | | | Soiling | Muzzle, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | C | . | . | . | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | . | . | Y | Y | . | . | . | . | . | . | Y | Y | . | . | . |
| | | 5551 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | . | . | . | . | . |
| | | | Soiling | Abdomen, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | Y | . | . | . | . | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | Y | Y | Y | Y | Y | Y |
| | | 5552 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5553 | No Abnormalities Detected | | X | X | . | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | | Soiling | Muzzle, General | . | . | C | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |

Severity Codes: X = Present; D = Decreased; F = Focal; S = Small; C = Clear; R = Red;
Y = Yellow; W = Wet; M = Minimal (10-30%); M = Moderate (31-60%);

Group 1 - 0mg/kg Group 2 - 50mg/kg Group 3 - 250mg/kg Group 4 - 500mg/kg

# Appendix A: Individual Clinical Observations – Male Rats

| Group | Sex | Animal | Clinical Sign | Site | Day numbers relative to Start Date 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | m | 5544 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | . | . |
| | | 5545 | No Abnormalities Detected | | X | X | . | . | . | . | . | . | . |
| | | | Skin, Excessive Hair Loss | | . | . | M | M | M | M | M | M | M |
| | | 5546 | No Abnormalities Detected | | X | X | X | X | . | X | . | X | X |
| | | | Soiling | Abdomen, General | . | . | . | . | . | . | . | . | . |
| | | | Soiling | Urogenital, General | . | . | . | . | Y | . | Y | . | . |
| | | 5547 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X |
| | | | Skin, Scab | Upper Back (Thoracic) | . | . | . | . | . | . | . | . | . |
| | | | Soiling | Muzzle, General | . | . | . | . | . | . | . | . | . |
| | | 5548 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X |
| | | 5549 | No Abnormalities Detected | | X | X | X | X | X | X | X | . | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | Y | Y |
| | | 5550 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X |
| | | | Soiling | Muzzle, General | . | . | . | . | . | . | . | . | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | . | . |
| | | 5551 | No Abnormalities Detected | | . | . | . | . | . | X | X | X | X |
| | | | Soiling | Abdomen, General | Y | . | . | . | . | . | . | . | . |
| | | | Soiling | Urogenital, General | Y | Y | Y | Y | Y | . | . | . | . |
| | | 5552 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X |
| | | 5553 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X |
| | | | Soiling | Muzzle, General | . | . | . | . | . | . | . | . | . |

Severity Codes: X = Present; D = Decreased; F = Focal; S = Small; C = Clear; R = Red;
Y = Yellow; W = Wet; M = Minimal (10-30%); M = Moderate (31-60%);

Group 1 - 0mg/kg Group 2 - 50mg/kg Group 3 - 250mg/kg Group 4 - 500mg/kg

# Appendix A: Individual Clinical Observations – Male Rats

Day numbers relative to Start Date

| Group | Sex | Animal | Clinical Sign | Site | -3 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 4 | M | 5574 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | . | . | X | X | X | X | X | X | X | X | X | X | X |
| | | | Soiling | Chin | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | . | . | Y | Y | . | . | . | . | . | . | . | . | . | . | . |
| | | 5575 | No Abnormalities Detected | | X | X | X | X | X | X | . | X | . | . | . | X | X | X | X | X | X | X | . | X | X | X |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | Y | . | Y | Y | Y | . | . | . | . | . | . | . | Y | . | . | . |
| | | 5576 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | . | . | . | . | . |
| | | | Missing Tooth | | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | | Soiling | Abdomen, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | Y | Y | Y | Y | Y | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | Y | Y | Y | Y | Y | Y |
| | | 5577 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | . | X | X | X | . | . | . | . | X | X |
| | | | Soiling | Abdomen, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | Y | Y | Y | . | . | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | . | . | . | . | . | R | . | . | . | Y | Y | Y | Y | . | . |
| | | 5578 | No Abnormalities Detected | | X | X | X | . | X | X | X | X | . | X | X | X | X | X | X | X | . | . | . | . | X | X |
| | | | Soiling | Urogenital, General | . | . | . | Y | . | . | . | . | Y | . | . | . | . | . | . | . | Y | Y | Y | Y | . | . |
| | | 5579 | No Abnormalities Detected | | X | X | X | X | X | X | X | . | . | . | X | X | X | X | X | X | . | . | . | . | . | X |
| | | | Soiling | Abdomen, General | . | . | . | . | . | . | . | Y | Y | Y | . | . | . | . | . | . | Y | Y | Y | Y | Y | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | Y | Y | Y | . | . | . | . | . | . | Y | Y | Y | Y | Y | . |
| | | 5580 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | . | . | . | . | . |
| | | | Soiling | Abdomen, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | Y | Y | . | . | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | Y | Y | Y | Y | Y | Y |
| | | 5581 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | . | . | . | . | . |
| | | | Soiling | Abdomen, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | Y | Y | Y | Y | Y | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | Y | Y | Y | Y | Y | Y |
| | | 5582 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | . | . | . | X | X |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | Y | Y | Y | Y | . | . |
| | | 5583 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | . | . | . | . | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | Y | Y | Y | Y | Y | Y |

Severity Codes: X = Present; D = Decreased; F = Focal; S = Small; C = Clear; R = Red;
Y = Yellow; W = Wet; M = Minimal (10-30%); M = Moderate (31-60%);

Group 1 - 0mg/kg Group 2 - 50mg/kg Group 3 - 250mg/kg Group 4 - 500mg/kg

# Appendix A: Individual Clinical Observations – Male Rats

Day numbers relative to Start Date

| Group | Sex | Animal | Clinical Sign | Site | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 4 | m | 5574 | No Abnormalities Detected | | X | . | . | . | . | . | . | . | X |
| | | | Soiling | Chin | . | . | . | . | R | . | . | . | . |
| | | | Soiling | Urogenital, General | . | Y | Y | Y | Y | Y | Y | Y | . |
| | | 5575 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | . | . |
| | | 5576 | No Abnormalities Detected | | X | X | X | X | . | . | . | . | . |
| | | | Missing Tooth | | . | . | . | . | . | X | X | X | X |
| | | | Soiling | Abdomen, General | . | . | . | . | . | . | . | . | . |
| | | | Soiling | Urogenital, General | . | . | . | . | Y | . | . | . | . |
| | | 5577 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X |
| | | | Soiling | Abdomen, General | . | . | . | . | . | . | . | . | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | . | . |
| | | 5578 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | . | . |
| | | 5579 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X |
| | | | Soiling | Abdomen, General | . | . | . | . | . | . | . | . | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | . | . |
| | | 5580 | No Abnormalities Detected | | X | X | X | X | . | . | X | X | X |
| | | | Soiling | Abdomen, General | . | . | . | . | . | . | . | . | . |
| | | | Soiling | Urogenital, General | . | . | . | . | Y | Y | . | . | . |
| | | 5581 | No Abnormalities Detected | | . | . | . | . | . | . | . | . | . |
| | | | Soiling | Abdomen, General | . | Y | . | . | . | . | . | . | . |
| | | | Soiling | Urogenital, General | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| | | 5582 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | . | . |
| | | 5583 | No Abnormalities Detected | | X | X | . | X | . | . | . | . | . |
| | | | Soiling | Urogenital, General | . | . | Y | . | Y | Y | Y | Y | Y |

Severity Codes: X = Present; D = Decreased; F = Focal; S = Small; C = Clear; R = Red;
Y = Yellow; W = Wet; M = Minimal (10-30%); M = Moderate (31-60%);

Group 1 - 0mg/kg Group 2 - 50mg/kg Group 3 - 250mg/kg Group 4 - 500mg/kg

# Appendix B: Individual Clinical Observations – Toxicity Group Female Rats

| | | | | | Day numbers relative to Start Date | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Group | Sex | Animal | Clinical Sign | Site | -3 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 |
| 1 | f | 5474 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5475 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5476 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5477 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5478 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5479 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5480 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5481 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5482 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5483 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

Severity Codes: X = Present; C = Clear; R = Red; Y = Yellow; W = Wet

Group 1 - 0mg/kg Group 2 - 50mg/kg Group 3 - 250mg/kg Group 4 - 500mg/kg

# Appendix B: Individual Clinical Observations – Toxicity Group Female Rats

| | | | | | Day numbers relative to Start Date | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Group | Sex | Animal | Clinical Sign | Site | 23 | 24 | 25 | 26 | 27 | 26 | 29 |
| 1 | f | 5474 | No Abnormalities Detected | | X | X | X | X | X | X | X |
| | | 5475 | No Abnormalities Detected | | X | X | X | X | X | X | X |
| | | 5476 | No Abnormalities Detected | | X | X | X | X | X | X | X |
| | | 5477 | No Abnormalities Detected | | X | X | X | X | X | X | X |
| | | 5478 | No Abnormalities Detected | | X | X | X | X | X | X | X |
| | | 5479 | No Abnormalities Detected | | X | X | X | X | X | X | X |
| | | 5480 | No Abnormalities Detected | | X | X | X | X | X | X | X |
| | | 5481 | No Abnormalities Detected | | X | X | X | X | X | X | X |
| | | 5482 | No Abnormalities Detected | | X | X | X | X | X | X | X |
| | | 5483 | No Abnormalities Detected | | X | X | X | X | X | X | X |

Severity Codes: X = Present; C = Clear; R = Red; Y = Yellow; W = Wet

Group 1 - 0mg/kg Group 2 - 50mg/kg Group 3 - 250mg/kg Group 4 - 500mg/kg

# Appendix B: Individual Clinical Observations – Toxicity Group Female Rats

Day numbers relative to Start Date

| Group | Sex | Animal | Clinical Sign | Site | -3 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | f | 5505 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5506 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5507 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5508 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5509 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5510 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5511 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5512 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5513 | No Abnormalities Detected | | X | X | X | X | X | . | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | | Soiling | Chin | . | . | . | . | . | C | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |

Severity Codes: X = Present; C = Clear; R = Red; Y = Yellow; W = Wet

Group 1 - 0mg/kg Group 2 - 50mg/kg Group 3 - 250mg/kg Group 4 - 500mg/kg

# Appendix B: Individual Clinical Observations – Toxicity Group Female Rats

| | | | | | Day numbers relative to Start Date | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Group | Sex | Animal | Clinical Sign | Site | 23 | 24 | 25 | 26 | 27 | 28 | 29 |
| 2 | f | 5505 | No Abnormalities Detected | | X | X | X | X | X | X | X |
| | | 5506 | No Abnormalities Detected | | X | X | X | X | X | X | X |
| | | 5507 | No Abnormalities Detected | | X | X | X | X | X | X | X |
| | | 5508 | No Abnormalities Detected | | X | X | X | X | X | X | X |
| | | 5509 | No Abnormalities Detected | | X | X | X | X | X | X | X |
| | | 5510 | No Abnormalities Detected | | X | X | X | X | X | X | X |
| | | 5511 | No Abnormalities Detected | | X | X | X | X | X | X | X |
| | | 5512 | No Abnormalities Detected | | X | X | X | X | X | X | X |
| | | 5513 | No Abnormalities Detected | | X | X | X | X | X | X | X |
| | | | Soiling | Chin | . | . | . | . | . | . | . |

Severity Codes: X = Present; C = Clear; R = Red; Y = Yellow; W = Wet

Group 1 - 0mg/kg Group 2 - 50mg/kg Group 3 - 250mg/kg Group 4 - 500mg/kg

# Appendix B: Individual Clinical Observations – Toxicity Group Female Rats

Day numbers relative to Start Date

| Group | Sex | Animal | Clinical Sign | Site | -3 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | f | 5534 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5535 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5536 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5537 | No Abnormalities Detected | | X | . | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | | Soiling | Muzzle, General | . | C | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | 5538 | No Abnormalities Detected | | X | X | X | X | X | . | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | | Soiling | Muzzle, General | . | . | . | . | . | C | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | 5539 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | . | . |
| | | | Soiling | Abdomen, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | Y | Y | Y |
| | | 5540 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5541 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5542 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5543 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | . | X | X | X | X | X | X | X | X | X |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | . | . | . | . | . | . | R | . | . | . | . | . | . | . | . | . |

Severity Codes: X = Present; C = Clear; R = Red; Y = Yellow; W = Wet

Group 1 - 0mg/kg Group 2 - 50mg/kg Group 3 - 250mg/kg Group 4 - 500mg/kg

# Appendix B: Individual Clinical Observations – Toxicity Group Female Rats

| | | | | | Day numbers relative to Start Date | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Group | Sex | Animal | Clinical Sign | Site | 23 | 24 | 25 | 26 | 27 | 28 | 29 |
| 3 | f | 5534 | No Abnormalities Detected | | X | X | X | X | X | X | X |
| | | 5535 | No Abnormalities Detected | | X | X | X | X | X | X | X |
| | | 5538 | No Abnormalities Detected | | X | X | X | X | X | X | X |
| | | 5537 | No Abnormalities Detected | | X | X | X | X | X | X | X |
| | | | Soiling | Muzzle, General | . | . | . | . | . | . | . |
| | | 5538 | No Abnormalities Detected | | X | X | X | X | X | X | X |
| | | | Soiling | Muzzle, General | . | . | . | . | . | . | . |
| | | 5539 | No Abnormalities Detected | | . | . | . | . | . | . | . |
| | | | Soiling | Abdomen, General | . | Y | Y | Y | Y | Y | Y |
| | | | Soiling | Urogenital, General | Y | Y | Y | Y | Y | . | . |
| | | 5540 | No Abnormalities Detected | | X | X | X | X | X | X | X |
| | | 5541 | No Abnormalities Detected | | X | X | X | X | X | X | X |
| | | 5542 | No Abnormalities Detected | | X | X | X | X | X | X | X |
| | | 5543 | No Abnormalities Detected | | X | X | X | X | X | X | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | Y |

Severity Codes: X = Present; C = Clear; R = Red; Y = Yellow; W = Wet

Group 1 - 0mg/kg Group 2 - 50mg/kg Group 3 - 250mg/kg Group 4 - 500mg/kg

# Appendix B: Individual Clinical Observations – Toxicity Group Female Rats

Day numbers relative to Start Date

| Group | Sex | Animal | Clinical Sign | Site | -3 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 4 | f | 5564 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5565 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5566 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5567 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | . | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | | Soiling | Muzzle, General | . | . | . | . | . | . | . | . | . | C | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | 5568 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | . | X | X | X | X | X | X | X | X | X | X |
| | | | Soiling | Nose | . | . | . | . | . | . | . | . | . | . | . | . | R | . | . | . | . | . | . | . | . | . | . |
| | | 5569 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5570 | No Abnormalities Detected | | X | X | . | . | . | . | . | . | . | . | . | X | X | X | . | . | . | . | . | . | . | . | X |
| | | | Respiration, Noisy | | . | . | . | . | W | W | W | W | W | W | W | . | . | . | . | . | . | . | . | . | . | . | . |
| | | | Respiration, Rapid | | . | . | . | . | X | X | X | X | X | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | | Soiling | Muzzle, General | . | . | C | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | | Soiling | Chin | . | . | . | . | . | . | . | . | . | . | . | . | . | . | R | R | R | R | R | R | R | R | . |
| | | | Soiling | Urogenital, General | . | . | . | Y | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | 5571 | No Abnormalities Detected | | X | X | X | X | X | X | X | . | X | X | X | X | X | X | X | X | X | . | . | X | X | X | . |
| | | | Soiling | Muzzle, General | . | . | . | . | . | . | . | C | . | . | . | . | . | . | . | . | . | . | R | . | . | . | R |
| | | | Soiling | Chin | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | R | . | . | . | . | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | 5572 | No Abnormalities Detected | | X | X | X | X | X | X | . | X | X | X | X | X | X | X | X | . | . | . | X | X | X | . | X |
| | | | Soiling | Muzzle, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | C | . | . | . | . | . | R | . |
| | | | Soiling | Chin | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | R | R | . | . | . | . | . |
| | | | Soiling | Abdomen, General | . | . | . | . | . | . | Y | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | 5573 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

Severity Codes: X = Present; C = Clear; R = Red; Y = Yellow; W = Wet

Group 1 - 0mg/kg Group 2 - 50mg/kg Group 3 - 250mg/kg Group 4 - 500mg/kg

# Appendix B: Individual Clinical Observations – Toxicity Group Female Rats

| | | | | | Day numbers relative to Start Date | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Group | Sex | Animal | Clinical Sign | Site | 23 | 24 | 25 | 26 | 27 | 28 | 29 |
| 4 | f | 5564 | No Abnormalities Detected | | X | X | X | X | X | X | X |
| | | 5565 | No Abnormalities Detected | | X | X | X | X | X | X | X |
| | | 5566 | No Abnormalities Detected | | X | X | X | X | X | X | X |
| | | 5567 | No Abnormalities Detected | | X | X | X | X | X | X | X |
| | | | Soiling | Muzzle, General | . | . | . | . | . | . | . |
| | | 5568 | No Abnormalities Detected | | X | X | X | X | X | X | X |
| | | | Soiling | Nose | . | . | . | . | . | . | . |
| | | 5569 | No Abnormalities Detected | | X | X | X | X | X | X | X |
| | | 5570 | No Abnormalities Detected | | . | . | . | . | . | X | X |
| | | | Respiration, Noisy | | . | . | . | . | . | . | . |
| | | | Respiration, Rapid | | . | . | . | . | . | . | . |
| | | | Soiling | Muzzle, General | . | . | . | . | . | . | . |
| | | | Soiling | Chin | R | R | R | R | R | . | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . |
| | | 5571 | No Abnormalities Detected | | . | X | X | . | X | X | X |
| | | | Soiling | Muzzle, General | . | . | . | . | . | . | . |
| | | | Soiling | Chin | . | . | . | R | . | . | . |
| | | | Soiling | Urogenital, General | Y | . | . | . | . | . | . |
| | | 5572 | No Abnormalities Detected | | X | X | X | . | . | . | X |
| | | | Soiling | Muzzle, General | . | . | . | . | . | . | . |
| | | | Soiling | Chin | . | . | . | R | R | R | . |
| | | | Soiling | Abdomen, General | . | . | . | . | . | . | . |
| | | 5573 | No Abnormalities Detected | | X | X | X | X | X | X | X |

Severity Codes: X = Present; C = Clear; R = Red; Y = Yellow; W = Wet

Group 1 - 0mg/kg Group 2 - 50mg/kg Group 3 - 250mg/kg Group 4 - 500mg/kg

# Appendix C: Individual Clinical Observations – Reproductive Group Female Rats

Day numbers relative to Start Date

| Group | Sex | Animal | Clinical Sign | Site | -3 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | f | 5494 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | | Skin, Excessive Hair Loss | | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | 5495 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5496 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5497 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5498 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | | Palpable Mass 1 | Axillary, Left | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | | Soiling | Muzzle, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | 5499 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | | Skin, Excessive Hair Loss | | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | 5500 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5501 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | | Soiling | Muzzle, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | 5502 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5503 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

Severity Codes: X = Present; F = Focal; 1 = Small; C = Clear; R = Red; Y = Yellow;
7 = Minimal (10-30%); 8 = Moderate (31-60%);

Group 1 - 0mg/kg Group 2 - 50mg/kg Group 3 - 250mg/kg Group 4 - 500mg/kg

# Appendix C: Individual Clinical Observations – Reproductive Group Female Rats

Day numbers relative to Start Date

| Group | Sex | Animal | Clinical Sign | Site | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | f | 5494 | No Abnormalities Detected | | X | X | X | X | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | X | . | . | . |
| | | | Skin, Excessive Hair Loss | | . | . | . | . | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | . | . | . |
| | | 5495 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | . |
| | | 5496 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | . |
| | | 5497 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . |
| | | 5498 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | . | X | . |
| | | | Palpable Mass 1 | Axillary, Left | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | 1 | 1 | . |
| | | | Soiling | Muzzle, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | C | . | . | . |
| | | 5499 | No Abnormalities Detected | | X | X | X | X | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | X | . |
| | | | Skin, Excessive Hair Loss | | . | . | . | . | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 8 | 7 | 8 | 8 | 8 | 8 | 8 | . |
| | | 5500 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | . | . |
| | | 5501 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | X | X | X |
| | | | Soiling | Muzzle, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | C | . | . | . |
| | | 5502 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5503 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | . | . |

Severity Codes: X = Present; F = Focal; 1 = Small; C = Clear; R = Red; Y = Yellow;
7 = Minimal (10-30%); 8 = Moderate (31-60%);

Group 1 - 0mg/kg Group 2 - 50mg/kg Group 3 - 250mg/kg Group 4 - 500mg/kg

# Appendix C: Individual Clinical Observations – Reproductive Group Female Rats

| Group | Sex | Animal | Clinical Sign | Site | Day numbers relative to Start Date 46 | 47 | 48 | 49 | 50 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | f | 5494 | No Abnormalities Detected | | . | . | . | . | . |
| | | | Skin, Excessive Hair Loss | | . | . | . | . | . |
| | | 5495 | No Abnormalities Detected | | . | . | . | . | . |
| | | 5496 | No Abnormalities Detected | | . | . | . | . | . |
| | | 5497 | No Abnormalities Detected | | . | . | . | . | . |
| | | 5498 | No Abnormalities Detected | | . | . | . | . | . |
| | | | Palpable Mass 1 | Axillary, Left | . | . | . | . | . |
| | | | Soiling | Muzzle, General | . | . | . | . | . |
| | | 5499 | No Abnormalities Detected | | . | . | . | . | . |
| | | | Skin, Excessive Hair Loss | | . | . | . | . | . |
| | | 5500 | No Abnormalities Detected | | . | . | . | . | . |
| | | 5501 | No Abnormalities Detected | | . | . | . | . | . |
| | | | Soiling | Muzzle, General | . | . | . | . | . |
| | | 5502 | No Abnormalities Detected | | X | X | . | . | . |
| | | 5503 | No Abnormalities Detected | | . | . | . | . | . |

Severity Codes: X = Present; F = Focal; 1 = Small; C = Clear; R = Red; Y = Yellow;
7 = Minimal (10-30%); 8 = Moderate (31-60%);

Group 1 - 0mg/kg Group 2 - 50mg/kg Group 3 - 250mg/kg Group 4 - 500mg/kg

# Appendix C: Individual Clinical Observations – Reproductive Group Female Rats

| Group | Sex | Animal | Clinical Sign | Site | Day numbers relative to Start Date | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | -3 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 |
| 2 | f | 5504 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5524 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5525 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5526 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5527 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5526 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | | Skin, Scab | Neck, Right | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | F | F | . | . | . | . |
| | | | Skin, Scab | Neck, Left | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | F | F | . | . | . | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | 5529 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5531 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5532 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5533 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

Severity Codes: X = Present; F = Focal; 1 = Small; C = Clear; R = Red; Y = Yellow;
7 = Minimal (10-30%); 8 = Moderate (31-60%);

Group 1 - 0mg/kg Group 2 - 50mg/kg Group 3 - 250mg/kg Group 4 - 500mg/kg

# Appendix C: Individual Clinical Observations – Reproductive Group Female Rats

| Group | Sex | Animal | Clinical Sign | Site | Day numbers relative to Start Date | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 |
| 2 | f | 5504 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | . |
| | | 5524 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | . |
| | | 5525 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | . |
| | | 5526 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | . |
| | | 5527 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | . | . |
| | | 5528 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | . |
| | | | Skin, Scab | Neck, Right | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | X | X | X | X |
| | | | Skin, Scab | Neck, Left | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | 5529 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | Y | . | . | . | . |
| | | 5531 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | . |
| | | 5532 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5533 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | . | . |

Severity Codes: X = Present; F = Focal; 1 = Small; C = Clear; R = Red; Y = Yellow;
7 = Minimal (10-30%); 8 = Moderate (31-60%);

Group 1 - 0mg/kg Group 2 - 50mg/kg Group 3 - 250mg/kg Group 4 - 500mg/kg

# Appendix C: Individual Clinical Observations – Reproductive Group Female Rats

| Group | Sex | Animal | Clinical Sign | Site | Day numbers relative to Start Date 46 | 47 | 48 | 49 | 50 |
|---|---|---|---|---|---|---|---|---|---|
| 2 | f | 55D4 | No Abnormalities Detected | | . | . | . | . | . |
| | | 5524 | No Abnormalities Detected | | . | . | . | . | . |
| | | 5525 | No Abnormalities Detected | | . | . | . | . | . |
| | | 5526 | No Abnormalities Detected | | . | . | . | . | . |
| | | 5527 | No Abnormalities Detected | | . | . | . | . | . |
| | | 5528 | No Abnormalities Detected | | X | . | . | . | . |
| | | | Skin, Scab | Neck, Right | . | . | . | . | . |
| | | | Skin, Scab | Neck, Left | . | . | . | . | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . |
| | | 5529 | No Abnormalities Detected | | . | . | . | . | . |
| | | 5531 | No Abnormalities Detected | | . | . | . | . | . |
| | | 5532 | No Abnormalities Detected | | . | . | . | . | . |
| | | 5533 | No Abnormalities Detected | | . | . | . | . | . |

Severity Codes: X = Present; F = Focal; 1 = Small; C = Clear; R = Red; Y = Yellow;
7 = Minimal (10-30%); 8 = Moderate (31-60%);

Group 1 - 0mg/kg Group 2 - 50mg/kg Group 3 - 250mg/kg Group 4 - 500mg/kg

# Appendix C: Individual Clinical Observations – Reproductive Group Female Rats

Day numbers relative to Start Date

| Group | Sex | Animal | Clinical Sign | Site | -3 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | f | 5554 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5555 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | | Soiling | Muzzle, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | 5556 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5557 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5558 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5559 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5560 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . | X | X | X | X | X | X | X | X | . | X | X | X |
| | | | Soiling | Muzzle, General | . | . | . | . | . | . | . | . | . | . | C | . | . | . | . | . | . | . | . | C | . | . | . |
| | | 5561 | No Abnormallties Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | . | . | X | X | X |
| | | | Soiling | Abdomen, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | Y | Y | Y | . | . | . |
| | | 5562 | No Abnormallties Detected | | X | X | X | X | . | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | | Skin, Scab | Muzzle, Right | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | | Soiling | Muzzle, General | . | . | . | . | C | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | 5563 | No Abnormalities Detected | | X | X | . | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | | Soiling | Muzzle, General | . | . | C | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |

Severity Codes: X = Present; F = Focal; 1 = Small; C = Clear; R = Red; Y = Yellow;
7 = Minimal (10-30%); 8 = Moderate (31-60%);

Group 1 - 0mg/kg Group 2 - 50mg/kg Group 3 - 250mg/kg Group 4 - 500mg/kg

# Appendix C: Individual Clinical Observations – Reproductive Group Female Rats

| | | | | | Day numbers relative to Start Date | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Group | Sex | Animal | Clinical Sign | Site | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 |
| 3 | f | 5554 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | . |
| | | 5555 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | . | X | X | X | X | X | X | X | X | X | . |
| | | | Soiling | Muzzle, General | . | . | . | . | . | . | . | . | . | . | . | . | C | . | . | . | . | . | . | . | . | . | . |
| | | 5556 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5557 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5558 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | . | . |
| | | 5559 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | . |
| | | 5560 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | . |
| | | | Soiling | Muzzle, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | 5561 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | | Soiling | Abdomen, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | 5562 | No Abnormalities Detected | | X | . | . | . | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | . |
| | | | Skin, Scab | Muzzle, Right | . | F | F | F | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | | Soiling | Muzzle, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | 5563 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | . |
| | | | Soiling | Muzzle, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |

Severity Codes: X = Present; F = Focal; 1 = Small; C = Clear; R = Red; Y = Yellow;
7 = Minimal (10-30%); 8 = Moderate (31-60%);

Group 1 - 0mg/kg Group 2 - 50mg/kg Group 3 - 250mg/kg Group 4 - 500mg/kg

# Appendix C: Individual Clinical Observations – Reproductive Group Female Rats

| Group | Sex | Animal | Clinical Sign | Site | Day numbers relative to Start Date 46 | 47 | 48 | 49 | 50 |
|---|---|---|---|---|---|---|---|---|---|
| 3 | f | 5554 | No Abnormalities Detected | | . | . | . | . | . |
| | | 5555 | No Abnormalities Detected | | . | . | . | . | . |
| | | | Soiling | Muzzle, General | . | . | . | . | . |
| | | 5556 | No Abnormalities Detected | | X | X | X | X | . |
| | | 5557 | No Abnormalities Detected | | X | . | . | . | . |
| | | 5558 | No Abnormalities Detected | | . | . | . | . | . |
| | | 5559 | No Abnormalities Detected | | . | . | . | . | . |
| | | 5560 | No Abnormalities Detected | | . | . | . | . | . |
| | | | Soiling | Muzzle, General | . | . | . | . | . |
| | | 5561 | No Abnormalities Detected | | . | . | . | . | . |
| | | | Soiling | Abdomen, General | . | . | . | . | . |
| | | 5562 | No Abnormalities Detected | | . | . | . | . | . |
| | | | Skin, Scab | Muzzle, Right | . | . | . | . | . |
| | | | Soiling | Muzzle, General | . | . | . | . | . |
| | | 5563 | No Abnormalities Detected | | . | . | . | . | . |
| | | | Soiling | Muzzle, General | . | . | . | . | . |

Severity Codes: X = Present; F = Focal; 1 = Small; C = Clear; R = Red; Y = Yellow;
7 = Minimal (10-30%); 8 = Moderate (31-60%);

Group 1 - 0mg/kg Group 2 - 50mg/kg Group 3 - 250mg/kg Group 4 - 500mg/kg

# Appendix C: Individual Clinical Observations – Reproductive Group Female Rats

Day numbers relative to Start Date

| Group | Sex | Animal | Clinical Sign | Site | -3 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 4 | f | 5584 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 5585 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | X | X | X | X | X | X |
| | | | Soiling | Muzzle, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | | Soiling | Chin | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | | Soiling | Abdomen, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | Y | . | . | . | . | . | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | Y | . | . | . | . | . | . |
| | | 5588 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | X | X | . | X |
| | | | Soiling | Muzzle, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | C | . |
| | | | Soiling | Abdomen, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | Y | . | . | . | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | Y | . | . | . | . |
| | | 5587 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | X | X | X | X | X |
| | | | Soiling | Abdomen, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | Y | . | . | . | . | . |
| | | 5588 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | . | . | . | . | X | X |
| | | | Soiling | Abdomen, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | Y | Y | . | . | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | Y | Y | Y | Y | Y | . | . |
| | | 5589 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . | X | X | X | X | X | X | X | . | . | X | X | X |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | . | . | . | Y | . | . | . | . | . | . | . | Y | Y | . | . | . |
| | | 5590 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | X | X | X | X | X | X |
| | | | Soiling | Abdomen, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | Y | . | . | . | . | . | . |
| | | 5591 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | X | X | X | X | X | X | X |
| | | | Soiling | Muzzle, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | | Soiling | Chin | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | R | . | . | . | . | . | . | . |
| | | 5592 | No Abnormalities Detected | | X | X | X | . | X | X | X | X | X | X | X | X | X | X | X | X | . | . | . | . | . | X | X |
| | | | Soiling | Nose | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | R | . | . | . | . | . | . |
| | | | Soiling | Back, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | Y | Y | Y | Y | . | . |
| | | | Soiling | Abdomen, General | . | . | . | Y | . | . | . | . | . | . | . | . | . | . | . | . | Y | Y | Y | Y | Y | . | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | Y | Y | Y | Y | Y | . | . |
| | | 5593 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | . | . | X | X | X | X |
| | | | Soiling | Abdomen, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | Y | Y | . | . | . | . | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | Y | Y | Y | . | . | . | . |

Severity Codes: X = Present; F = Focal; 1 = Small; C = Clear; R = Red; Y = Yellow;
7 = Minimal (10-30%); 8 = Moderate (31-60%);

Group 1 - 0mg/kg Group 2 - 50mg/kg Group 3 - 250mg/kg Group 4 - 500mg/kg

# Appendix C: Individual Clinical Observations – Reproductive Group Female Rats

Day numbers relative to Start Date

| Group | Sex | Animal | Clinical Sign | Site | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 4 | f | 5584 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . | . |
| | | 5585 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | . | X | X | X | . | X | X | X | . | X | X |
| | | | Soiling | Muzzle, General | . | . | . | . | . | . | . | . | . | . | . | . | C | . | . | . | . | . | . | . | C | . | . |
| | | | Soiling | Chin | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | R | . | . | . | . | . | . |
| | | | Soiling | Abdomen, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | 5586 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | | Soiling | Muzzle, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | | Soiling | Abdomen, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | 5587 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | | Soiling | Abdomen, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | 5588 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | | Soiling | Abdomen, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | 5589 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | 5590 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . |
| | | | Soiling | Abdomen, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | 5591 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | | Soiling | Muzzle, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | | Soiling | Chin | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | 5592 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | | Soiling | Nose | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | | Soiling | Back, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | | Soiling | Abdomen, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | 5593 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | . |
| | | | Soiling | Abdomen, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |

Severity Codes: X = Present; F = Focal; 1 = Small; C = Clear; R = Red; Y = Yellow;
7 = Minimal (10-30%); 8 = Moderate (31-60%);

Group 1 - 0mg/kg Group 2 - 50mg/kg Group 3 - 250mg/kg Group 4 - 500mg/kg

# Appendix C: Individual Clinical Observations – Reproductive Group Female Rats

| | | | | | Day numbers relative to Start Date | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | Sex | Animal | Clinical Sign | Site | 46 | 47 | 48 | 49 | 50 |
| 4 | f | 5584 | No Abnormalities Detected | | . | . | . | . | . |
| | | 5585 | No Abnormalities Detected | | X | . | . | . | . |
| | | | Soiling | Muzzle, General | . | . | . | . | . |
| | | | Soiling | Chin | . | . | . | . | . |
| | | | Soiling | Abdomen, General | . | . | . | . | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . |
| | | 5586 | No Abnormalities Detected | | X | . | . | . | . |
| | | | Soiling | Muzzle, General | . | . | . | . | . |
| | | | Soiling | Abdomen, General | . | . | . | . | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . |
| | | 5587 | No Abnormalities Detected | | . | . | . | . | . |
| | | | Soiling | Abdomen, General | . | . | . | . | . |
| | | 5588 | No Abnormalities Detected | | X | . | . | . | . |
| | | | Soiling | Abdomen, General | . | . | . | . | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . |
| | | 5589 | No Abnormalities Detected | | X | X | . | . | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . |
| | | 5590 | No Abnormalities Detected | | . | . | . | . | . |
| | | | Soiling | Abdomen, General | . | . | . | . | . |
| | | 5591 | No Abnormalities Detected | | . | X | X | . | X |
| | | | Soiling | Muzzle, General | C | . | . | C | . |
| | | | Soiling | Chin | . | . | . | . | . |
| | | 5592 | No Abnormalities Detected | | X | . | . | . | . |
| | | | Soiling | Nose | . | . | . | . | . |
| | | | Soiling | Back, General | . | . | . | . | . |
| | | | Soiling | Abdomen, General | . | . | . | . | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . |
| | | 5593 | No Abnormalities Detected | | . | . | . | . | . |
| | | | Soiling | Abdomen, General | . | . | . | . | . |
| | | | Soiling | Urogenital, General | . | . | . | . | . |

Severity Codes: X = Present; F = Focal; 1 = Small; C = Clear; R = Red; Y = Yellow;
7 = Minimal (10-30%); 8 = Moderate (31-80%);

Group 1 - 0mg/kg Group 2 - 50mg/kg Group 3 - 250mg/kg Group 4 - 500mg/kg

# Appendix D: Individual Body Weights (grams) – Male Rats

| Group Sex | Animal Number | Day numbers relative to Start Date -8 | 1 | 8 | 15 | 22 | 29 | 30 |
|---|---|---|---|---|---|---|---|---|
| 1m | 5484 | 253.5 | 324.3 | 361.5 | 402.6 | 442.6 | 491.0 | 462.8 |
| | 5485 | 252.0 | 299.6 | 336.2 | 369.9 | 397.2 | 423.4 | 399.4 |
| | 5486 | 236.7 | 301.4 | 341.5 | 377.5 | 411.3 | 436.6 | 414.2 |
| | 5487 | 243.9 | 309.6 | 351.5 | 397.4 | 435.4 | 467.1 | 447.0 |
| | 5488 | 238.8 | 304.2 | 353.9 | 406.0 | 442.6 | 465.9 | 442.3 |
| | 5489 | 231.5 | 306.0 | 352.6 | 386.4 | 432.4 | 461.8 | 440.4 |
| | 5490 | 249.1 | 323.9 | 370.3 | 409.7 | 442.4 | 473.6 | 451.0 |
| | 5491 | 234.3 | 301.9 | 353.4 | 399.9 | 440.8 | 470.4 | 447.6 |
| | 5492 | 244.6 | 311.3 | 344.6 | 369.1 | 393.9 | 407.0 | 390.1 |
| | 5493 | 254.5 | 319.5 | 358.5 | 391.2 | 412.8 | 430.9 | 413.5 |
| | Mean | 243.89 | 310.17 | 352.40 | 390.97 | 425.14 | 452.77 | 430.83 |
| | S.D. | 8.31 | 9.35 | 9.93 | 14.75 | 19.47 | 26.59 | 24.54 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix D: Individual Body Weights (grams) – Male Rats

| Group Sex | Animal Number | Day numbers relative to Start Date -8 | 1 | 8 | 15 | 22 | 29 | 30 |
|---|---|---|---|---|---|---|---|---|
| 2m | 5514 | 235.4 | 295.4 | 335.1 | 350.0 | 359.3 | 377.5 | 355.8 |
| | 5515 | 255.7 | 304.5 | 350.0 | 398.1 | 426.9 | 449.1 | 428.6 |
| | 5516 | 244.2 | 317.5 | 358.0 | 394.6 | 436.1 | 456.7 | 434.9 |
| | 5517 | 244.3 | 325.1 | 377.5 | 416.6 | 455.6 | 475.6 | 454.2 |
| | 5518 | 236.4 | 306.9 | 352.1 | 395.2 | 438.6 | 471.8 | 441.7 |
| | 5519 | 253.5 | 324.9 | 359.8 | 395.9 | 436.3 | 457.8 | 434.6 |
| | 5520 | 253.3 | 313.6 | 353.9 | 385.7 | 396.8 | 419.3 | 393.1 |
| | 5521 | 247.5 | 309.8 | 353.5 | 391.2 | 427.9 | 451.6 | 430.7 |
| | 5522 | 239.6 | 303.2 | 354.1 | 402.4 | 449.6 | 474.8 | 453.2 |
| | 5523 | 232.4 | 304.2 | 326.7 | 358.5 | 384.0 | 407.4 | 388.3 |
| | Mean | 244.23 | 310.51 | 352.07 | 388.82 | 421.11 | 444.16 | 421.51 |
| | S.D. | 8.24 | 9.72 | 13.69 | 20.02 | 30.97 | 32.54 | 31.96 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix D: Individual Body Weights (grams) – Male Rats

| Group Sex | Animal Number | Day numbers relative to Start Date -8 | 1 | 8 | 15 | 22 | 29 | 30 |
|---|---|---|---|---|---|---|---|---|
| 3m | 5544 | 233.3 | 291.3 | 334.0 | 376.6 | 411.7 | 442.4 | 422.5 |
| | 5545 | 236.5 | 305.4 | 357.4 | 393.2 | 418.1 | 458.3 | 434.0 |
| | 5546 | 248.2 | 313.4 | 373.4 | 417.3 | 460.4 | 480.4 | 455.5 |
| | 5547 | 245.7 | 314.8 | 363.5 | 411.3 | 434.3 | 461.1 | 440.1 |
| | 5548 | 251.7 | 305.6 | 324.9 | 369.2 | 420.9 | 456.9 | 426.8 |
| | 5549 | 239.1 | 306.4 | 360.8 | 402.0 | 437.0 | 470.4 | 449.5 |
| | 5550 | 232.0 | 286.7 | 334.4 | 361.5 | 382.4 | 408.1 | 389.1 |
| | 5551 | 254.3 | 302.6 | 333.4 | 368.8 | 394.4 | 415.2 | 400.4 |
| | 5552 | 255.6 | 306.1 | 348.3 | 366.8 | 388.4 | 413.3 | 392.8 |
| | 5553 | 244.0 | 301.1 | 323.7 | 362.0 | 390.7 | 412.3 | 391.5 |
| | Mean | 244.04 | 303.34 | 345.38 | 382.87 | 413.83 | 441.84 | 420.22 |
| | S.D. | 8.56 | 8.73 | 17.60 | 21.19 | 25.26 | 27.30 | 25.11 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix D: Individual Body Weights (grams) – Male Rats

| Group Sex | Animal Number | Day numbers relative to Start Date -8 | 1 | 8 | 15 | 22 | 29 | 30 |
|---|---|---|---|---|---|---|---|---|
| 4m | 5574 | 247.3 | 295.2 | 331.0 | 357.8 | 374.5 | 391.9 | 375.5 |
| | 5575 | 232.5 | 284.3 | 321.8 | 341.1 | 357.9 | 383.1 | 363.7 |
| | 5576 | 250.8 | 313.2 | 349.9 | 384.1 | 413.6 | 374.5 | 372.9 |
| | 5577 | 242.4 | 302.5 | 353.4 | 393.4 | 431.2 | 455.0 | 429.3 |
| | 5578 | 252.0 | 330.9 | 363.9 | 400.0 | 430.3 | 452.8 | 433.5 |
| | 5579 | 253.5 | 312.7 | 344.0 | 377.2 | 395.7 | 413.1 | 394.2 |
| | 5580 | 237.4 | 311.1 | 347.4 | 365.0 | 389.2 | 409.6 | 386.0 |
| | 5581 | 255.4 | 325.6 | 382.7 | 414.6 | 428.8 | 449.4 | 427.7 |
| | 5582 | 236.2 | 303.2 | 344.1 | 380.8 | 403.4 | 420.4 | 401.7 |
| | 5583 | 244.2 | 322.8 | 370.5 | 405.7 | 424.5 | 450.8 | 427.5 |
| | Mean | 245.17 | 310.15 | 350.87 | 381.97 | 404.91 | 420.06 | 401.20 |
| | S.D. | 7.94 | 14.32 | 18.01 | 22.74 | 25.46 | 30.72 | 26.61 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix E: Individual Body Weights (grams) – Toxicity Group Female Rats

| Group Sex | Animal Number | Day numbers relative to Start Date -8 | 1 | 3 | 8 | 15 | 22 | 28 | 29 |
|---|---|---|---|---|---|---|---|---|---|
| 1f | 5474 | 174.7 | 207.7 | . | 226.6 | 232.3 | 245.5 | 252.0 | 235.7 |
| | 5475 | 182.5 | 216.4 | . | 246.3 | 263.6 | 283.5 | 292.2 | 276.4 |
| | 5476 | 167.0 | 196.6 | . | 209.0 | 225.4 | 245.5 | 250.8 | 236.1 |
| | 5477 | 170.8 | 196.7 | . | 217.5 | 231.2 | 249.9 | 261.4 | 244.2 |
| | 5478 | 192.7 | 227.9 | . | 251.1 | 276.9 | 306.4 | 310.4 | 295.3 |
| | 5479 | 183.8 | 227.9 | . | 252.6 | 281.0 | 296.3 | 302.9 | 287.7 |
| | 5480 | 185.5 | 210.9 | . | 229.4 | 250.8 | 281.9 | 280.7 | 267.7 |
| | 5481 | 190.2 | 225.3 | . | 250.8 | 274.3 | 281.7 | 293.8 | 276.9 |
| | 5482 | 175.4 | 199.1 | . | 214.1 | 225.8 | 251.4 | 264.5 | 247.1 |
| | 5483 | 178.3 | 205.4 | . | 213.3 | 223.8 | 236.7 | 238.5 | 226.5 |
| | Mean | 180.09 | 211.39 | . | 231.27 | 248.49 | 267.88 | 274.72 | 259.56 |
| | S.D. | 8.31 | 12.47 | . | 17.79 | 23.55 | 24.70 | 24.62 | 24.11 |
| | N | 10 | 10 | 0 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix E: Individual Body Weights (grams) – Toxicity Group Female Rats

| Group Sex | Animal Number | Day numbers relative to Start Date -8 | 1 | 3 | 8 | 15 | 22 | 28 | 29 |
|---|---|---|---|---|---|---|---|---|---|
| 2f | 5505 | 179.6 | 209.5 | . | 220.2 | 236.3 | 244.4 | 254.3 | 242.3 |
| | 5506 | 173.6 | 197.1 | . | 207.1 | 220.3 | 239.6 | 253.5 | 238.1 |
| | 5507 | 184.7 | 211.8 | . | 230.8 | 249.8 | 266.4 | 277.4 | 261.0 |
| | 5508 | 186.3 | 218.1 | . | 236.0 | 251.3 | 282.1 | 269.3 | 269.6 |
| | 5509 | 176.8 | 209.6 | . | 230.7 | 254.4 | 281.2 | 292.5 | 276:5 |
| | 5510 | 183.6 | 212.0 | . | 235.8 | 256.6 | 277.8 | 278.7 | 287.3 |
| | 5511 | 170.6 | 207.7 | . | 223.3 | 231.8 | 249.0 | 257.4 | 237.2 |
| | 5512 | 169.4 | 199.1 | . | 201.5 | 213.6 | 226.0 | 236.0 | 224.6 |
| | 5513 | 194.2 | 231.7 | . | 255.7 | 271.4 | 297.5 | 305.5 | 290.3 |
| | 5530 | 190.0 | 229.5 | 230.2 | . | . | . | . | . |
| | Mean | 180.90 | 212.61 | 230.20 | 226.79 | 242.83 | 262.67 | 271.62 | 256.32 |
| | S.D. | 8.29 | 11.29 | . | 16.26 | 18.66 | 23.91 | 22.56 | 21.74 |
| | N | 10 | 10 | 1 | 9 | 9 | 9 | 9 | 9 |

Group 1 - Dmg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix E: Individual Body Weights (grams) – Toxicity Group Female Rats

| Group Sex | Animal Number | Day numbers relative to Start Date -8 | 1 | 3 | 8 | 15 | 22 | 28 | 29 |
|---|---|---|---|---|---|---|---|---|---|
| 3f | 5534 | 171.9 | 192.6 | . | 216.9 | 231.6 | 255.7 | 262.1 | 252.4 |
| | 5535 | 174.7 | 194.9 | . | 208.4 | 225.8 | 228.6 | 237.4 | 225.7 |
| | 5536 | 176.1 | 209.2 | . | 234.4 | 255.7 | 273.9 | 279.2 | 268.7 |
| | 5537 | 179.3 | 212.9 | . | 233.0 | 243.1 | 258.8 | 268.3 | 256.7 |
| | 5538 | 167.9 | 192.2 | . | 212.7 | 229.9 | 246.9 | 255.7 | 237.6 |
| | 5539 | 185.8 | 224.4 | . | 244.9 | 278.3 | 300.2 | 292.5 | 279.8 |
| | 5540 | 198.8 | 225.6 | . | 243.4 | 265.0 | 269.9 | 275.0 | 259.6 |
| | 5541 | 181.3 | 218.3 | . | 237.7 | 249.2 | 270.3 | 274.3 | 258.6 |
| | 5542 | 184.5 | 214.9 | . | 235.6 | 252.8 | 262.5 | 275.6 | 264.0 |
| | 5543 | 197.2 | 232.1 | . | 245.0 | 266.9 | 282.8 | 284.4 | 276.8 |
| | Mean | 181.75 | 211.71 | . | 231.20 | 249.83 | 284.96 | 270.45 | 257.99 |
| | S.D. | 10.17 | 14.37 | . | 13.62 | 17.41 | 19.64 | 15.65 | 16.58 |
| | N | 10 | 10 | 0 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix E: Individual Body Weights (grams) – Toxicity Group Female Rats

| Group Sex | Animal Number | Day numbers relative to Start Date -8 | 1 | 3 | 8 | 15 | 22 | 28 | 29 |
|---|---|---|---|---|---|---|---|---|---|
| 4f | 5564 | 171.4 | 198.2 | . | 221.4 | 238.3 | 246.2 | 249.7 | 236.1 |
| | 5565 | 169.5 | 192.6 | . | 210.0 | 229.8 | 234.1 | 240.9 | 230.3 |
| | 5566 | 184.4 | 216.8 | . | 252.2 | 265.8 | 276.7 | 290.4 | 271.7 |
| | 5567 | 178.6 | 202.7 | . | 221.8 | 231.2 | 232.3 | 248.5 | 235.5 |
| | 5568 | 177.3 | 202.3 | . | 222.9 | 244.8 | 254.1 | 267.0 | 255.2 |
| | 5569 | 185.9 | 222.5 | . | 242.3 | 257.6 | 267.5 | 282.2 | 259.2 |
| | 5570 | 173.5 | 190.6 | . | 202.7 | 222.6 | 232.7 | 249.0 | 233.2 |
| | 5571 | 194.2 | 231.2 | . | 278.1 | 289.0 | 299.9 | 304.9 | 292.4 |
| | 5572 | 188.7 | 223.9 | . | 247.4 | 265.6 | 288.8 | 291.3 | 280.1 |
| | 5573 | 181.6 | 209.4 | . | 224.0 | 247.3 | 259.4 | 264.3 | 251.0 |
| | Mean | 180.53 | 209.02 | . | 232.28 | 249.20 | 259.17 | 268.82 | 254.47 |
| | S.D. | 7.94 | 14.01 | . | 22.58 | 20.41 | 23.94 | 22.18 | 21.50 |
| | N | 10 | 10 | 0 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix F: Individual Body Weights (grams) – Reproductive Group Female Rats

| Group Sex | Animal Number | 1 | 8 | 15 | 22 | GD0 | GD7 | GD14 | GD20 | PP1 | PP4 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1f | 5494 | 213.0 | 229.3 | 244.8 | | 246.4 | 288.1 | 330.1 | 422.0 | 320.0 | 346.8 |
| | 5495 | 208.4 | 231.1 | 253.0 | | 256.7 | 288.3 | 323.6 | 423.0 | 298.8 | 326.5 |
| | 5496 | 217.1 | 239.7 | 260.2 | | 265.7 | 295.7 | 336.8 | 433.5 | 319.6 | 336.2 |
| | 5497 | 221.6 | 244.5 | 260.5 | | 277.1 | 299.8 | 343.6 | 432.6 | 332.3 | 346.3 |
| | 5498 | 200.5 | 231.9 | 252.6 | | 251.9 | 285.5 | 324.1 | 408.1 | 306.3 | 315.6 |
| | 5499 | 219.9 | 244.9 | 265.0 | | 278.6 | 309.0 | 354.3 | 445.5 | 342.3 | 353.0 |
| | 5500 | 200.3 | 215.3 | 240.1 | | 240.0 | 277.0 | 328.8 | 429.0 | 339.9 | 343.7 |
| | 5501 | 205.5 | 224.4 | 234.0 | | 244.7 | 280.3 | 290.5 | 297.9 | 302.4 | A |
| | 5502 | 210.2 | 240.3 | 257.0 | | 275.9 | 313.6 | 358.2 | 447.5 | 344.7 | 357.0 |
| | 5503 | 206.4 | 226.3 | 250.5 | | 252.7 | 289.6 | 328.3 | 427.1 | 322.6 | 336.1 |
| | Mean | 210.3 | 232.8 | 251.8 | | 259.0 | 292.7 | 331.8 | 416.6 | 322.9 | 340.1 |
| | S.D. | 7.5 | 9.6 | 9.7 | | 14.4 | 11.9 | 18.9 | 43.2 | 16.7 | 13.1 |
| | N | 10 | 10 | 10 | | 10 | 10 | 10 | 10 | 10 | 9 |

A = Evidence of Copulation, not pregnant

# Appendix F: Individual Body Weights (grams) – Reproductive Group Female Rats

| Group Sex | Animal Number | 1 | 8 | 15 | 22 | GD0 | GD7 | GD14 | GD20 | PP1 | PP4 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2f | 5504 | 228.3 | 248.7 | 273.1 | | 281.1 | 298.7 | 339.4 | 440.1 | 331.2 | 364.4 |
| | 5524 | 202.9 | 219.8 | 231.8 | | 242.9 | 279.5 | 325.3 | 406.4 | 308.6 | 334.9 |
| | 5525 | 211.2 | 224.9 | 234.0 | | 239.8 | 265.5 | 298.6 | 385.3 | 282.3 | 300.1 |
| | 5526 | 197.5 | 220.7 | 229.4 | | 229.3 | 253.3 | 291.4 | 375.5 | 300.2 | 304.1 |
| | 5527 | 233.5 | 251.9 | 284.0 | | 281.0 | 321.3 | 371.9 | 454.8 | 352.6 | 360.3 |
| | 5528 | 212.1 | 222.2 | 227.2 | | 246.6 | 271.4 | 316.3 | 415.5 | 291.4 | 296.6 |
| | 5529 | 201.6 | 214.8 | 231.7 | | 249.0 | 276.4 | 307.5 | 386.1 | 305.6 | 321.5 |
| | 5531 | 200.7 | 213.4 | 223.0 | | 248.4 | 283.7 | 332.6 | 434.9 | 336.3 | 329.4 |
| | 5532 | 216.1 | 234.9 | 256.1 | | 258.8 | 289.9 | 335.9 | 448.3 | 324.4 | 361.4 |
| | 5533 | 213.0 | 231.1 | 251.4 | | 255.0 | 270.9 | 289.3 | 305.7 | 316.8 | A |
| | Mean | 211.7 | 228.2 | 244.2 | | 253.2 | 281.1 | 320.8 | 405.3 | 314.9 | 330.3 |
| | S.D. | 11.9 | 13.4 | 21.0 | | 16.8 | 19.0 | 25.6 | 44.8 | 21.6 | 27.1 |
| | N | 10 | 10 | 10 | | 10 | 10 | 10 | 10 | 10 | 9 |

A = Evidence of Copulation, not pregnant

# Appendix F: Individual Body Weights (grams) – Reproductive Group Female Rats

| Group Sex | Animal Number | 1 | 8 | 15 | 22 | GD0 | GD7 | GD14 | GD20 | PP1 | PP4 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 3f | 5554 | 197.1 | 224.2 | 241.1 | | 245.8 | 282.0 | 330.4 | 413.1 | 310.0 | 313.3 |
| | 5555 | 217.0 | 225.7 | 250.5 | | 244.4 | 273.6 | 308.6 | 379.3 | 299.3 | 309.8 |
| | 5556 | 222.2 | 240.9 | 257.8 | 274.9 | 270.2 | 297.0 | 332.7 | 415.2 | 311.5 | 320.2 |
| | 5557 | 217.0 | 234.9 | 252.8 | | 267.6 | 303.1 | 346.3 | 438.3 | 332.5 | 352.8 |
| | 5558 | 226.7 | 241.2 | 268.1 | | 270.7 | 297.6 | 343.2 | 452.7 | 342.4 | 343.9 |
| | 5559 | 227.1 | 264.9 | 274.3 | | 276.8 | 306.2 | 348.5 | 442.3 | 329.7 | 355.3 |
| | 5560 | 203.5 | 220.5 | 246.2 | | 256.0 | 274.2 | 321.1 | 406.8 | 311.9 | 323.1 |
| | 5561 | 210.6 | 227.4 | 231.2 | | 250.2 | 262.5 | 275.5 | 274.1 | 284.9 | A |
| | 5562 | 204.9 | 231.2 | 255.1 | | 252.9 | 272.4 | 304.2 | 384.9 | 291.9 | 300.6 |
| | 5563 | 235.5 | 253.7 | 274.2 | | 279.0 | 325.4 | 375.5 | 481.7 | 356.4 | 373.1 |
| | Mean | 216.2 | 236.5 | 255.1 | | 261.4 | 289.4 | 328.6 | 408.8 | 317.1 | 332.5 |
| | S.D. | 12.1 | 14.1 | 14.1 | | 12.9 | 19.5 | 27.9 | 56.7 | 22.8 | 24.6 |
| | N | 10 | 10 | 10 | | 10 | 10 | 10 | 10 | 10 | 9 |

A = Evidence of Copulation, not pregnant

# Appendix F: Individual Body Weights (grams) – Reproductive Group Female Rats

| Group Sex | Animal Number | 1 | 8 | 15 | 22 | GD0 | GD7 | GD14 | GD20 | PP1 | PP4 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 4f | 5584 | 208.4 | 222.9 | 235.2 | | 233.8 | 268.3 | 294.8 | 339.0 | 294.9 | 310.5 |
| | 5585 | 202.5 | 230.4 | 235.0 | | 253.5 | 287.5 | 326.2 | 421.7 | 308.9 | 316.3 |
| | 5586 | 210.7 | 235.6 | 249.3 | | 267.0 | 296.0 | 335.6 | 449.1 | 305.9 | 341.8 |
| | 5587 | 221.3 | 247.1 | 262.1 | | 268.6 | 294.1 | 331.7 | 411.5 | 312.7 | 342.3 |
| | 5588 | 216.6 | 233.6 | 250.7 | | 253.0 | 288.9 | 328.0 | 362.7 | 314.5 | 334.2 |
| | 5589 | 191.6 | 212.3 | 218.9 | | 229.9 | 260.5 | 283.5 | 359.7 | 273.3 | 300.8 |
| | 5590 | 209.5 | 220.8 | 239.9 | | 251.2 | 291.5 | 313.7 | 405.2 | 287.6 | 323.8 |
| | 5591 | 197.8 | 206.6 | 212.5 | 230.6 | 224.9 | 257.3 | 279.2 | 358.6 | 257.8 | 272.1 |
| | 5592 | 218.7 | 246.2 | 268.7 | | 280.4 | 308.7 | 344.0 | 429.8 | 310.6 | 349.6 |
| | 5593 | 227.3 | 259.3 | 276.3 | | 289.7 | 311.5 | 341.9 | 430.4 | 327.1 | 351.5 |
| | Mean | 210.4 | 231.5 | 244.9 | | 255.2 | 286.4 | 317.9 | 396.8 | 299.3 | 324.3 |
| | S.D. | 11.0 | 16.4 | 20.7 | | 21.6 | 18.7 | 24.0 | 38.3 | 21.1 | 25.0 |
| | N | 10 | 10 | 10 | | 10 | 10 | 10 | 10 | 10 | 10 |

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# Appendix G: Individual Body Weight Gain (grams) – Male Rats

Sex: Male

Body Weight Gain (Grams)

| 0mg/kg | Day(s) Relative to Start Date | | | | |
|---|---|---|---|---|---|
| | 1 → 8 | 8 → 15 | 15 → 22 | 22 → 29 | 1 → 29 |
| 5484 | 37.2 | 41.1 | 40.0 | 48.4 | 166.7 |
| 5485 | 36.6 | 33.7 | 27.3 | 26.2 | 123.8 |
| 5486 | 40.1 | 36.0 | 33.8 | 25.3 | 135.2 |
| 5487 | 41.9 | 45.9 | 38.0 | 31.7 | 157.5 |
| 5488 | 49.7 | 52.1 | 36.6 | 23.3 | 161.7 |
| 5489 | 46.6 | 33.8 | 46.0 | 29.4 | 155.8 |
| 5490 | 46.4 | 39.4 | 32.7 | 31.2 | 149.7 |
| 5491 | 51.5 | 46.5 | 40.9 | 29.6 | 168.5 |
| 5492 | 33.3 | 24.5 | 24.8 | 13.1 | 95.7 |
| 5493 | 39.0 | 32.7 | 21.6 | 18.1 | 111.4 |
| Mean | 42.23 | 38.57 | 34.17 | 27.63 | 142.60 |
| SD | 6.06 | 8.11 | 7.71 | 9.40 | 25.04 |
| N | 10 | 10 | 10 | 10 | 10 |

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# Appendix G: Individual Body Weight Gain (grams) – Male Rats

Sex: Male

Body Weight Gain (Grams)

| 50mg/kg | Day(s) Relative to Start Date | | | | |
|---|---|---|---|---|---|
| | 1 → 8 | 8 → 15 | 15 → 22 | 22 → 29 | 1 → 29 |
| 5514 | 39.7 | 14.9 | 9.3 | 18.2 | 82.1 |
| 5515 | 45.5 | 48.1 | 28.8 | 22.2 | 144.6 |
| 5516 | 40.5 | 36.6 | 41.5 | 20.6 | 139.2 |
| 5517 | 52.4 | 39.1 | 39.0 | 20.0 | 150.5 |
| 5518 | 45.2 | 43.1 | 43.4 | 33.2 | 164.9 |
| 5519 | 34.9 | 36.1 | 40.4 | 21.5 | 132.9 |
| 5520 | 40.3 | 31.8 | 11.1 | 22.5 | 105.7 |
| 5521 | 43.7 | 37.7 | 36.7 | 23.7 | 141.8 |
| 5522 | 50.9 | 48.3 | 47.2 | 25.2 | 171.6 |
| 5523 | 22.5 | 31.8 | 25.5 | 23.4 | 103.2 |
| Mean | 41.56 | 36.75 | 32.29 | 23.05 | 133.65 |
| SD | 8.51 | 9.64 | 13.32 | 4.09 | 28.45 |
| N | 10 | 10 | 10 | 10 | 10 |

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# Appendix G: Individual Body Weight Gain (grams) – Male Rats

Sex: Male

Body Weight Gain (Grams)

| 250mg/kg | Day(s) Relative to Start Date | | | | |
|---|---|---|---|---|---|
| | 1 → 8 | 8 → 15 | 15 → 22 | 22 → 29 | 1 → 29 |
| 5544 | 42.7 | 42.6 | 35.1 | 30.7 | 151.1 |
| 5545 | 52.0 | 35.8 | 24.9 | 40.2 | 152.9 |
| 5546 | 60.0 | 43.9 | 43.1 | 20.0 | 167.0 |
| 5547 | 48.7 | 47.8 | 23.0 | 26.8 | 146.3 |
| 5548 | 19.3 | 44.3 | 51.7 | 36.0 | 151.3 |
| 5549 | 54.4 | 41.2 | 35.0 | 33.4 | 164.0 |
| 5550 | 47.7 | 27.1 | 20.9 | 25.7 | 121.4 |
| 5551 | 30.8 | 35.4 | 25.6 | 20.8 | 112.6 |
| 5552 | 42.2 | 18.5 | 21.6 | 24.9 | 107.2 |
| 5553 | 22.6 | 38.3 | 28.7 | 21.6 | 111.2 |
| Mean | 42.04 | 37.49 | 30.96 | 28.01 | 138.50 |
| SD | 13.63 | 8.88 | 10.19 | 6.85 | 22.95 |
| N | 10 | 10 | 10 | 10 | 10 |

# Appendix G: Individual Body Weight Gain (grams) – Male Rats

Sex: Male  Body Weight Gain (Grams)

| 500mg/kg | Day(s) Relative to Start Date | | | | |
|---|---|---|---|---|---|
| | 1 → 8 | 8 → 15 | 15 → 22 | 22 → 29 | 1 → 29 |
| 5574 | 35.8 | 26.8 | 16.7 | 17.4 | 96.7 |
| 5575 | 37.5 | 19.3 | 16.8 | 25.2 | 98.8 |
| 5576 | 36.7 | 34.2 | 29.5 | -39.1 | 61.3 |
| 5577 | 50.9 | 40.0 | 37.8 | 23.8 | 152.5 |
| 5578 | 33.0 | 36.1 | 30.3 | 22.5 | 121.9 |
| 5579 | 31.3 | 33.2 | 18.5 | 17.4 | 100.4 |
| 5580 | 36.3 | 17.6 | 24.2 | 20.4 | 98.5 |
| 5581 | 57.1 | 31.9 | 14.2 | 20.6 | 123.8 |
| 5582 | 40.9 | 36.7 | 22.6 | 17.0 | 117.2 |
| 5583 | 47.7 | 35.2 | 18.8 | 26.3 | 128.0 |
| Mean | 40.72 | 31.10 | 22.94 | 15.15 | 109.91 |
| SD | 8.43 | 7.51 | 7.52 | 19.34 | 24.52 |
| N | 10 | 10 | 10 | 10 | 10 |

# Appendix H: Individual Body Weight Gain (grams) – Toxicity Group Female Rats

Sex: Female Body Weight Gain (Grams)

| 0mg/kg | Day(s) Relative to Start Date | | | | |
|---|---|---|---|---|---|
| | 1 → 8 | 8 → 15 | 15 → 22 | 22 → 28 | 1 → 28 |
| 5474 | 18.9 | 5.7 | 13.2 | 6.5 | 44.3 |
| 5475 | 31.9 | 15.3 | 19.9 | 8.7 | 75.8 |
| 5476 | 12.4 | 16.4 | 20.1 | 5.3 | 54.2 |
| 5477 | 20.8 | 13.7 | 18.7 | 11.5 | 64.7 |
| 5478 | 23.2 | 25.8 | 29.5 | 4.0 | 82.5 |
| 5479 | 24.7 | 28.4 | 15.3 | 6.6 | 75.0 |
| 5480 | 18.5 | 21.4 | 31.1 | -1.2 | 69.8 |
| 5481 | 25.5 | 23.5 | 7.4 | 12.1 | 68.5 |
| 5482 | 15.0 | 11.5 | 25.8 | 13.1 | 65.4 |
| 5483 | 7.9 | 10.5 | 12.9 | 1.8 | 33.1 |
| Mean | 19.88 | 17.22 | 19.39 | 6.84 | 63.33 |
| SD | 6.97 | 7.32 | 7.62 | 4.63 | 15.25 |
| N | 10 | 10 | 10 | 10 | 10 |

# Appendix H: Individual Body Weight Gain (grams) – Toxicity Group Female Rats

Sex: Female Body Weight Gain (Grams)

| 50mg/kg | Day(s) Relative to Start Date | | | | |
|---|---|---|---|---|---|
| | 1 → 8 | 8 → 15 | 15 → 22 | 22 → 28 | 1 → 28 |
| 5505 | 10.7 | 16.1 | 8.1 | 9.9 | 44.8 |
| 5506 | 10.0 | 13.2 | 19.3 | 13.9 | 56.4 |
| 5507 | 19.0 | 19.0 | 16.6 | 11.0 | 65.6 |
| 5508 | 17.9 | 15.3 | 30.8 | 7.2 | 71.2 |
| 5509 | 21.1 | 23.7 | 26.8 | 11.3 | 82.9 |
| 5510 | 23.8 | 20.8 | 21.2 | 0.9 | 66.7 |
| 5511 | 15.6 | 8.5 | 17.2 | 8.4 | 49.7 |
| 5512 | 2.4 | 12.1 | 12.4 | 10.0 | 36.9 |
| 5513 | 24.0 | 15.7 | 26.1 | 8.0 | 73.8 |
| Mean | 16.06 | 16.04 | 19.83 | 8.96 | 60.89 |
| SD | 7.18 | 4.63 | 7.25 | 3.63 | 14.97 |
| N | 9 | 9 | 9 | 9 | 9 |

# Appendix H: Individual Body Weight Gain (grams) – Toxicity Group Female Rats

Sex: Female Body Weight Gain (Grams)

| 250mg/kg | Day(s) Relative to Start Date | | | | |
|---|---|---|---|---|---|
| | 1 → 8 | 8 → 15 | 15 → 22 | 22 → 28 | 1 → 28 |
| 5534 | 24.3 | 14.7 | 24.1 | 6.4 | 69.5 |
| 5535 | 13.5 | 17.4 | 2.8 | 8.8 | 42.5 |
| 5536 | 25.2 | 21.3 | 18.2 | 5.3 | 70.0 |
| 5537 | 20.1 | 10.1 | 15.7 | 9.5 | 55.4 |
| 5538 | 20.5 | 17.2 | 17.0 | 8.8 | 63.5 |
| 5539 | 20.5 | 33.4 | 21.9 | -7.7 | 68.1 |
| 5540 | 17.8 | 21.6 | 4.9 | 5.1 | 49.4 |
| 5541 | 19.4 | 11.5 | 21.1 | 4.0 | 56.0 |
| 5542 | 20.7 | 17.2 | 9.7 | 13.1 | 60.7 |
| 5543 | 12.9 | 21.9 | 15.9 | 1.6 | 52.3 |
| Mean | 19.49 | 18.63 | 15.13 | 5.49 | 58.74 |
| SD | 3.97 | 6.58 | 7.16 | 5.66 | 9.24 |
| N | 10 | 10 | 10 | 10 | 10 |

# Appendix H: Individual Body Weight Gain (grams) – Toxicity Group Female Rats

Sex: Female Body Weight Gain (Grams)

| 500mg/kg | Day(s) Relative to Start Date | | | | |
|---|---|---|---|---|---|
| | 1 → 8 | 8 → 15 | 15 → 22 | 22 → 28 | 1 → 28 |
| 5564 | 23.2 | 16.9 | 7.9 | 3.5 | 51.5 |
| 5565 | 17.4 | 19.8 | 4.3 | 6.8 | 48.3 |
| 5566 | 35.4 | 13.6 | 10.9 | 13.7 | 73.6 |
| 5567 | 19.1 | 9.4 | 1.1 | 16.2 | 45.8 |
| 5568 | 20.6 | 21.9 | 9.3 | 12.9 | 64.7 |
| 5569 | 19.8 | 15.3 | 9.9 | 14.7 | 59.7 |
| 5570 | 12.1 | 19.9 | 10.1 | 16.3 | 58.4 |
| 5571 | 46.9 | 10.9 | 10.9 | 5.0 | 73.7 |
| 5572 | 23.5 | 18.2 | 23.2 | 2.5 | 67.4 |
| 5573 | 14.6 | 23.3 | 12.1 | 4.9 | 54.9 |
| Mean | 23.26 | 16.92 | 9.97 | 9.65 | 59.80 |
| SD | 10.42 | 4.80 | 5.74 | 5.59 | 9.94 |
| N | 10 | 10 | 10 | 10 | 10 |

# Appendix I: Individual Body Weight Gain (grams) – Reproductive Group Female Rats

| Group Sex | Animal Number | 1-8 | 8-15 | 15-22 | GD0-GD7 | GD7-GD14 | GD14-GD20 | PP0-PP4 |
|---|---|---|---|---|---|---|---|---|
| 1f | 5494 | 16.3 | 15.5 | | 41.7 | 42.0 | 91.9 | 26.8 |
| | 5495 | 22.7 | 21.9 | | 31.6 | 35.3 | 99.4 | 27.7 |
| | 5496 | 22.6 | 20.5 | | 30.0 | 41.1 | 96.7 | 16.6 |
| | 5497 | 22.9 | 16.0 | | 22.7 | 43.8 | 89.0 | 14.0 |
| | 5498 | 31.4 | 20.7 | | 33.6 | 38.6 | 84.0 | 9.3 |
| | 5499 | 25.0 | 20.1 | | 30.4 | 45.3 | 91.2 | 10.7 |
| | 5500 | 15.0 | 24.8 | | 37.0 | 51.8 | 100.2 | 3.8 |
| | 5501 | 18.9 | 9.6 | | 35.6 | 10.2 | 7.4 | evidence of copulation, not pregnant |
| | 5502 | 30.1 | 16.7 | | 37.7 | 44.6 | 89.3 | 12.3 |
| | 5503 | 19.9 | 24.2 | | 36.9 | 38.7 | 98.8 | 13.5 |
| | Mean | 22.5 | 19.0 | | 33.7 | 39.1 | 84.8 | 15.0 |
| | S.D. | 5.4 | 4.6 | | 5.3 | 11.1 | 24.3 | 7.8 |
| | N | 10 | 10 | | 10 | 10 | 10 | 9 |

A = Evidence of Copulation, not pregnant

# Appendix I: Individual Body Weight Gain (grams) – Reproductive Group Female Rats

| Group Sex | Animal Number | 1-8 | 8-15 | 15-22 | GD0-GD7 | GD7-GD14 | GD14-GD20 | PP0-PP4 |
|---|---|---|---|---|---|---|---|---|
| 2f | 5504 | 20.4 | 24.4 | | 17.6 | 40.7 | 100.7 | 33.2 |
| | 5524 | 16.9 | 12.0 | | 36.6 | 45.8 | 81.1 | 26.3 |
| | 5525 | 13.7 | 9.1 | | 25.7 | 33.1 | 86.7 | 17.8 |
| | 5526 | 23.2 | 8.7 | | 24.0 | 38.1 | 84.1 | 3.9 |
| | 5527 | 18.4 | 32.1 | | 40.3 | 50.6 | 82.9 | 7.7 |
| | 5528 | 10.1 | 5.0 | | 24.8 | 44.9 | 99.2 | 5.2 |
| | 5529 | 13.2 | 16.9 | | 27.4 | 31.1 | 78.6 | 15.9 |
| | 5531 | 12.7 | 9.6 | | 35.3 | 48.9 | 102.3 | -6.9 |
| | 5532 | 18.8 | 21.2 | | 31.1 | 46.0 | 112.4 | 37.0 |
| | 5533 | 18.1 | 20.3 | | 15.9 | 18.4 | 16.4 | evidence of copulation, not pregnant |
| | Mean | 16.6 | 15.9 | | 27.9 | 39.8 | 84.4 | 15.6 |
| | S.D. | 4.0 | 8.5 | | 8.0 | 9.9 | 26.4 | 14.6 |
| | N | 10 | 10 | | 10 | 10 | 10 | 9 |

A = Evidence of Copulation, not pregnant

# Appendix I: Individual Body Weight Gain (grams) – Reproductive Group Female Rats

| Group Sex | Animal Number | 1-8 | 8-15 | 15-22 | GD0-GD7 | GD7-GD14 | GD14-GD20 | PP0-PP4 |
|---|---|---|---|---|---|---|---|---|
| 3f | 5554 | 27.1 | 16.9 | | 36.2 | 48.4 | 82.7 | 3.3 |
| | 5555 | 8.7 | 24.8 | | 29.2 | 35.0 | 70.7 | 10.5 |
| | 5556 | 18.7 | 16.9 | 17.1 | 26.8 | 35.7 | 82.5 | 8.7 |
| | 5557 | 17.9 | 17.9 | | 35.5 | 43.2 | 92.0 | 20.3 |
| | 5558 | 14.5 | 26.9 | | 26.9 | 45.6 | 109.5 | 1.5 |
| | 5559 | 37.8 | 9.4 | | 29.4 | 42.3 | 93.8 | 25.6 |
| | 5560 | 17.0 | 25.7 | | 18.2 | 46.9 | 85.7 | 11.2 |
| | 5561 | 16.8 | 3.8 | | 12.3 | 13.0 | -1.4 | evidence of copulation, not pregnant |
| | 5562 | 26.3 | 23.9 | | 19.5 | 31.8 | 80.7 | 8.7 |
| | 5563 | 18.2 | 20.5 | | 46.4 | 50.1 | 106.2 | 16.7 |
| | Mean | 20.3 | 18.7 | | 28.0 | 39.2 | 80.2 | 11.8 |
| | S.D. | 8.1 | 7.4 | | 9.9 | 11.1 | 31.0 | 7.8 |
| | N | 10 | 10 | | 10 | 10 | 10 | 9 |

A = Evidence of Copulation, not pregnant

# Appendix I: Individual Body Weight Gain (grams) – Reproductive Group Female Rats

| Group Sex | Animal Number | 1-8 | 8-15 | 15-22 | GD0-GD7 | GD7-GD14 | GD14-GD20 | PP0-PP4 |
|---|---|---|---|---|---|---|---|---|
| 4f | 5584 | 14.5 | 12.3 | | 34.5 | 26.5 | 44.2 | 15.6 |
| | 5585 | 27.9 | 4.6 | | 34.0 | 38.7 | 95.5 | 7.4 |
| | 5586 | 24.9 | 13.7 | | 29.0 | 39.6 | 113.5 | 35.9 |
| | 5587 | 25.8 | 15.0 | | 25.5 | 37.6 | 79.8 | 29.6 |
| | 5588 | 17.0 | 17.1 | | 35.9 | 39.1 | 34.7 | 19.7 |
| | 5589 | 20.7 | 6.6 | | 30.6 | 23.0 | 76.2 | 27.5 |
| | 5590 | 11.3 | 19.1 | | 40.3 | 22.2 | 91.5 | 36.2 |
| | 5591 | 8.8 | 5.9 | 18.1 | 32.4 | 21.9 | 79.4 | 14.3 |
| | 5592 | 27.5 | 22.5 | | 28.3 | 35.3 | 85.8 | 39.0 |
| | 5593 | 32.0 | 17.0 | | 21.8 | 30.4 | 88.5 | 24.4 |
| | Mean | 21.0 | 13.4 | | 31.2 | 31.4 | 78.9 | 25.0 |
| | S.D. | 7.8 | 6.0 | | 5.4 | 7.5 | 23.4 | 10.6 |
| | N | 10 | 10 | | 10 | 10 | 10 | 10 |

A = Evidence of Copulation, not pregnant

# Appendix J: Individual Food Consumption (grams/animal/day) – Male Rats

Day numbers relative to Start Date

| Group | Sex | Cage | No In Cage | From: To: | 1 8 | 5 8 | 8 15 |
|---|---|---|---|---|---|---|---|
| 1 | m | 5484 | 1 | | . | 24.0 | 22.7 |
| | | 5485 | 1 | | . | 23.8 | 22.9 |
| | | 5486 | 1 | | 25.5 | . | 23.8 |
| | | 5487 | 1 | | 29.3 | . | 28.5 |
| | | 5488 | 1 | | 28.5 | . | 28.1 |
| | | 5489 | 1 | | . | 24.3 | 23.7 |
| | | 5490 | 1 | | . | 25.0 | 23.4 |
| | | 5491 | 1 | | . | 26.5 | 25.8 |
| | | 5492 | 1 | | . | 25.2 | 23.5 |
| | | 5493 | 1 | | . | 26.5 | 24.3 |
| | | | | | --- | --- | --- |
| | | | | Mean | 27.77 | 25.05 | 24.65 |
| | | | | S.D. | 1.97 | 1.12 | 2.11 |
| | | | | N | 3 | 7 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix J: Individual Food Consumption (grams/animal/day) – Male Rats

Day numbers relative to Start Date

| Group | Sex | Cage | No In Cage | From: To: | 1 8 | 5 8 | 8 15 |
|---|---|---|---|---|---|---|---|
| 2 | m | 5514 | 1 | | 23.2 | . | 19.9 |
| | | 5515 | 1 | | 24.9 | . | 26.8 |
| | | 5516 | 1 | | 25.9 | . | 24.0 |
| | | 5517 | 1 | | 30.6 | . | 29.2 |
| | | 5518 | 1 | | 26.2 | . | 25.5 |
| | | 5519 | 1 | | 26.9 | . | 26.3 |
| | | 5520 | 1 | | 25.0 | . | 25.9 |
| | | 5521 | 1 | | 25.7 | . | 25.9 |
| | | 5522 | 1 | | 27.6 | . | 27.0 |
| | | 5523 | 1 | | 23.5 | . | 23.1 |
| | | | | | ---- | ---- | ---- |
| | | | | Mean | 25.95 | . | 25.35 |
| | | | | S.D. | 2.13 | . | 2.54 |
| | | | | N | 10 | . | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix J: Individual Food Consumption (grams/animal/day) – Male Rats

Day numbers relative to Start Date

| Group | Sex | Cage | No In Cage | From: To: | 1 8 | 5 8 | 8 15 |
|---|---|---|---|---|---|---|---|
| 3 | m | 5544 | 1 | | 25.1 | . | 26.8 |
| | | 5545 | 1 | | 28.3 | . | 26.6 |
| | | 5546 | 1 | | 29.4 | . | 28.4 |
| | | 5547 | 1 | | 27.4 | . | 25.2 |
| | | 5548 | 1 | | 22.6 | . | 26.1 |
| | | 5549 | 1 | | 26.0 | . | 25.8 |
| | | 5550 | 1 | | 24.3 | . | 23.4 |
| | | 5551 | 1 | | 21.0 | . | 22.0 |
| | | 5552 | 1 | | 24.5 | . | 21.4 |
| | | 5553 | 1 | | 24.3 | . | 23.7 |
| | | | | | --- | --- | --- |
| | | | | Mean | 25.31 | . | 24.94 |
| | | | | S.D. | 2.57 | . | 2.26 |
| | | | | N | 10 | . | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix J: Individual Food Consumption (grams/animal/day) – Male Rats

Day numbers relative to Start Date

| Group | Sex | Cage | No In Cage | From: To: | 1 8 | 5 8 | 8 15 |
|---|---|---|---|---|---|---|---|
| 4 | m | 5574 | 1 | | 22.4 | . | 20.9 |
| | | 5575 | 1 | | 22.5 | . | 20.0 |
| | | 5576 | 1 | | 24.5 | . | 23.3 |
| | | 5577 | 1 | | 23.2 | . | 23.4 |
| | | 5578 | 1 | | 24.3 | . | 23.3 |
| | | 5579 | 1 | | 21.3 | . | 19.7 |
| | | 5580 | 1 | | 21.8 | . | 20.9 |
| | | 5581 | 1 | | 28.0 | . | 25.7 |
| | | 5582 | 1 | | 22.3 | . | 23.8 |
| | | 5583 | 1 | | 27.0 | . | 25.3 |
| | | | | | --- | --- | --- |
| | | | | Mean | 23.72 | . | 22.64 |
| | | | | S.D. | 2.24 | . | 2.14 |
| | | | | N | 10 | . | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix K: Individual Food Consumption (grams/animal/day) – Toxicity Group Female Rats

Day numbers relative to Start Date

| Group | Sex | Cage | No In Cage | From: To: | 1 8 | 5 8 | 8 15 | 15 22 | 22 28 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | f | 5474 | 1 | | . | 16.4 | 16.2 | 15.9 | 14.5 |
| | | 5475 | 1 | | . | 22.1 | 20.3 | 19.4 | 18.5 |
| | | 5476 | 1 | | . | 15.5 | 17.6 | 18.8 | 15.5 |
| | | 5477 | 1 | | . | 15.5 | 15.3 | 15.9 | 14.1 |
| | | 5478 | 1 | | . | 25.2 | 24.1 | 24.9 | 25.0 |
| | | 5479 | 1 | | . | 17.2 | 21.4 | 20.0 | 16.8 |
| | | 5480 | 1 | | . | 21.6 | 20.7 | 21.8 | 16.6 |
| | | 5481 | 1 | | . | 19.2 | 18.4 | 18.6 | 18.5 |
| | | 5482 | 1 | | . | 17.4 | 17.8 | 19.9 | 19.1 |
| | | 5483 | 1 | | . | 17.7 | 20.1 | 20.5 | 16.4 |
| | | | | | ---- | ---- | ---- | ---- | ---- |
| | | | | Mean | . | 18.78 | 19.19 | 19.56 | 17.49 |
| | | | | S.D. | . | 3.22 | 2.63 | 2.67 | 3.12 |
| | | | | N | . | 10 | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix K: Individual Food Consumption (grams/animal/day) – Toxicity Group Female Rats

Day numbers relative to Start Date

| Group | Sex | Cage | No In Cage | From: To: | 1 8 | 5 8 | 8 15 | 15 22 | 22 28 |
|---|---|---|---|---|---|---|---|---|---|
| 2 | f | 5505 | 1 | | 14.7 | . | 17.0 | 16.7 | 15.1 |
| | | 5506 | 1 | | 14.8 | . | 15.7 | 17.4 | 14.6 |
| | | 5507 | 1 | | 16.3 | . | 17.2 | 17.4 | 16.7 |
| | | 5508 | 1 | | 19.8 | . | 20.0 | 21.6 | 17.6 |
| | | 5509 | 1 | | 19.8 | . | 18.8 | 19.1 | 19.5 |
| | | 5510 | 1 | | 17.0 | . | 17.8 | 17.4 | 18.7 |
| | | 5511 | 1 | | 17.2 | . | 16.9 | 17.6 | 16.6 |
| | | 5512 | 1 | | 14.3 | . | 15.0 | 14.8 | 15.7 |
| | | 5513 | 1 | | 20.4 | . | 19.0 | 20.1 | 18.7 |
| | | | | | --- | --- | --- | --- | --- |
| | | | | Mean | 17.14 | . | 17.50 | 18.02 | 17.00 |
| | | | | S.D. | 2.36 | . | 1.60 | 1.99 | 1.73 |
| | | | | N | 9 | . | 9 | 9 | 9 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix K: Individual Food Consumption (grams/animal/day) – Toxicity Group Female Rats

Day numbers relative to Start Date

| Group | Sex | Cage | No In Cage | From: To: | 1 8 | 5 8 | 8 15 | 15 22 | 22 28 |
|---|---|---|---|---|---|---|---|---|---|
| 3 | f | 5534 | 1 | | 16.5 | . | 16.7 | 17.4 | 16.3 |
| | | 5535 | 1 | | 14.9 | . | 14.8 | 13.3 | 12.5 |
| | | 5536 | 1 | | 18.7 | . | 19.7 | 19.9 | 18.2 |
| | | 5537 | 1 | | 16.2 | . | 17.7 | 18.0 | 17.2 |
| | | 5538 | 1 | | 19.1 | . | 19.9 | 18.7 | 18.6 |
| | | 5539 | 1 | | 19.7 | . | 21.6 | 20.1 | 17.1 |
| | | 5540 | 1 | | 18.0 | . | 18.9 | 17.2 | 16.8 |
| | | 5541 | 1 | | 18.4 | . | 18.7 | 18.4 | 16.5 |
| | | 5542 | 1 | | 17.3 | . | 17.6 | 16.8 | 15.7 |
| | | 5543 | 1 | | 18.5 | . | 20.4 | 17.8 | 17.3 |
| | | | | | --- | --- | --- | --- | --- |
| | | | | Mean | 17.74 | . | 18.59 | 17.75 | 16.61 |
| | | | | S.D. | 1.50 | . | 1.98 | 1.90 | 1.67 |
| | | | | N | 10 | . | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix K: Individual Food Consumption (grams/animal/day) – Toxicity Group Female Rats

Day numbers relative to Start Date

| Group | Sex | Cage | No In Cage | From: To: | 1 8 | 5 8 | 8 15 | 15 22 | 22 28 |
|---|---|---|---|---|---|---|---|---|---|
| 4 | f | 5564 | 1 | | 16.4 | . | 17.8 | 15.8 | 13.9 |
| | | 5565 | 1 | | 14.5 | . | 17.8 | 17.2 | 12.9 |
| | | 5566 | 1 | | 19.6 | . | 18.9 | 18.7 | 16.6 |
| | | 5567 | 1 | | 16.0 | . | 16.6 | 15.9 | 16.0 |
| | | 5568 | 1 | | 17.2 | . | 19.9 | 18.5 | 18.4 |
| | | 5569 | 1 | | 18.6 | . | 22.8 | 20.9 | 19.3 |
| | | 5570 | 1 | | 13.9 | . | 15.7 | 17.0 | 15.9 |
| | | 5571 | 1 | | 20.8 | . | 18.6 | 17.6 | 17.3 |
| | | 5572 | 1 | | 18.3 | . | 17.9 | 17.9 | 17.2 |
| | | 5573 | 1 | | 17.7 | . | 19.1 | 19.2 | 16.9 |
| | | | | | --- | --- | --- | --- | --- |
| | | | | Mean | 17.29 | . | 18.51 | 17.85 | 16.43 |
| | | | | S.D. | 2.16 | . | 1.94 | 1.53 | 1.93 |
| | | | | N | 10 | . | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix L: Individual Food Consumption (grams/animal/day) – Reproductive Group Female Rats

| | | food consumption (g/day) | | | | | |
|---|---|---|---|---|---|---|---|
| Group Sex | Animal Number | Days 1-8 | Days 8-15 | Gestation Days 0-7 | Gestation Days 7-14 | Gestation Days 14-20 | Post Partum Days 0-4 |
| 1f | 5494 | 16.4 | 17.0 | 19.7 | 19.9 | 22.7 | 30.6 |
| | 5495 | 16.5 | 17.6 | 18.1 | 18.4 | 20.1 | 34.0 |
| | 5496 | 19.7 | 19.0 | 19.0 | 20.9 | 24.5 | 40.4 |
| | 5497 | 18.3 | 18.9 | 16.9 | 19.4 | 22.0 | 35.5 |
| | 5498 | 19.2 | 19.5 | 17.8 | 19.6 | 22.8 | 35.4 |
| | 5499 | 19.3 | 18.8 | 21.1 | 22.5 | 24.2 | 33.5 |
| | 5500 | 16.5 | 17.3 | 19.4 | 20.9 | 23.3 | 30.6 |
| | 5501 | 17.6 | 18.8 | 19.8 | 19.8 | 17.9 | A |
| | 5502 | 20.1 | 19.0 | 20.9 | 23.4 | 23.7 | 36.2 |
| | 5503 | 18.5 | 20.2 | 20.2 | 21.6 | 25.5 | 38.6 |
| | Mean | 18.2 | 18.6 | 19.3 | 20.6 | 22.7 | 35.0 |
| | S.D. | 1.40 | 1.01 | 1.36 | 1.53 | 2.24 | 3.27 |
| | N | 10 | 10 | 10 | 10 | 10 | 9 |

A = Evidence of Copulation, not pregnant

# Appendix L: Individual Food Consumption (grams/animal/day) – Reproductive Group Female Rats

| | | food consumption (g/day) | | | | | |
|---|---|---|---|---|---|---|---|
| Group Sex | Animal Number | Days 1-8 | Days 8-15 | Gestation Days 0-7 | Gestation Days 7-14 | Gestation Days 14-20 | Post Partum Days 0-4 |
| 2f | 5504 | 21.9 | 22.4 | 18.3 | 21.7 | 24.5 | 42.6 |
| | 5524 | 17.7 | 17.1 | 20.5 | 21.9 | 22.1 | 34.8 |
| | 5525 | 18.0 | 17.3 | 17.7 | 18.7 | 21.2 | 34.8 |
| | 5526 | 16.5 | 15.5 | 13.3 | 20.1 | 22.5 | 25.4 |
| | 5527 | 21.0 | 22.1 | 22.5 | 24.1 | 25.8 | 36.0 |
| | 5528 | 17.3 | 19.1 | 18.8 | 18.9 | 25.4 | 33.4 |
| | 5529 | 16.8 | 18.1 | 20.0 | 19.3 | 21.8 | 34.0 |
| | 5531 | 16.6 | 15.4 | 18.2 | 21.1 | 25.4 | 29.9 |
| | 5532 | 20.7 | 20.4 | 20.0 | 23.3 | 25.9 | 43.0 |
| | 5533 | 19.3 | 19.3 | 17.6 | 17.7 | 16.4 | A |
| | Mean | 18.6 | 18.7 | 18.7 | 20.7 | 23.1 | 34.9 |
| | S.D. | 2.00 | 2.46 | 2.42 | 2.09 | 2.98 | 5.53 |
| | N | 10 | 10 | 10 | 10 | 10 | 9 |

A = Evidence of Copulation, not pregnant

# Appendix L: Individual Food Consumption (grams/animal/day) – Reproductive Group Female Rats

| | | food consumption (g/day) | | | | | |
|---|---|---|---|---|---|---|---|
| Group Sex | Animal Number | Days 1-8 | Days 8-15 | Gestation Days 0-7 | Gestation Days 7-14 | Gestation Days 14-20 | Post Partum Days 0-4 |
| 3f | 5554 | 17.4 | 17.7 | 19.4 | 21.8 | 22.8 | 31.1 |
| | 5555 | 17.7 | 19.7 | 17.0 | 18.8 | 21.6 | 22.9 |
| | 5556 | 21.1 | 22.0 | 17.6 | 18.6 | 21.2 | 29.6 |
| | 5557 | 20.8 | 21.0 | 20.5 | 22.7 | 25.2 | 39.5 |
| | 5558 | 19.6 | 20.3 | 19.5 | 20.6 | 24.1 | 30.6 |
| | 5559 | 21.7 | 20.3 | 18.7 | 21.0 | 25.3 | 35.5 |
| | 5560 | 19.2 | 19.3 | 17.0 | 19.2 | 24.6 | 30.2 |
| | 5561 | 18.0 | 16.1 | 13.8 | 12.7 | 12.1 | A |
| | 5562 | 19.1 | 20.7 | 15.7 | 17.1 | 21.3 | 29.8 |
| | 5563 | 19.5 | 21.4 | 21.3 | 23.9 | 26.9 | 40.7 |
| | Mean | 19.4 | 19.9 | 18.1 | 19.6 | 22.5 | 32.2 |
| | S.D. | 1.46 | 1.78 | 2.28 | 3.19 | 4.13 | 5.52 |
| | N | 10 | 10 | 10 | 10 | 10 | 9 |

A = Evidence of Copulation, not pregnant

# Appendix L: Individual Food Consumption (grams/animal/day) – Reproductive Group Female Rats

| | | food consumption (g/day) | | | | | |
|---|---|---|---|---|---|---|---|
| Group Sex | Animal Number | Days 1-8 | Days 8-15 | Gestation Days 0-7 | Gestation Days 7-14 | Gestation Days 14-20 | Post Partum Days 0-4 |
| 4f | 5584 | 16.0 | 16.2 | 17.1 | 17.0 | 17.5 | 24.3 |
| | 5585 | 15.5 | 15.2 | 18.0 | 19.4 | 23.7 | 29.9 |
| | 5586 | 18.7 | 19.1 | 20.4 | 19.6 | 23.4 | 37.4 |
| | 5587 | 16.9 | 18.8 | 16.5 | 20.0 | 22.2 | 39.8 |
| | 5588 | 18.2 | 16.3 | 17.9 | 20.7 | 21.5 | 21.2 |
| | 5589 | 16.7 | 15.6 | 15.1 | 16.0 | 20.5 | 30.1 |
| | 5590 | 17.6 | 18.7 | 20.5 | 19.3 | 24.9 | 39.4 |
| | 5591 | 13.1 | 14.4 | 14.7 | 15.5 | 17.7 | 24.7 |
| | 5592 | 20.7 | 19.8 | 20.2 | 20.7 | 25.9 | 39.0 |
| | 5593 | 22.6 | 20.2 | 19.5 | 19.5 | 24.7 | 39.2 |
| | Mean | 17.6 | 17.4 | 18.0 | 18.8 | 22.2 | 32.5 |
| | S.D. | 2.68 | 2.10 | 2.15 | 1.90 | 2.93 | 7.30 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 |

# DOW CORNING CORPORATION
# HEALTH & ENVIRONMENTAL SCIENCES

## CONTRIBUTING SCIENTIST REPORT

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| | |
|---|---|
| **Report Title:** | Functional Observational Battery (FOB) and Motor Activity Evaluation Results for a Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test for Dimethylsilanediol (DMSD), ZMAT 4065555 in Sprague-Dawley Rats via Oral Gavage |
| **HES Study Number:** | 10872-102 |
| **Test Article:** | Dimethylsilanediol (DMSD) |
| **Contributing Scientist:** | Teresa A. Cortner, B.G.S.<br>HES Toxicologist |
| **Study Director:** | Jeanne Domoradzki, Ph.D., D.A.B.T.<br>Toxicology Specialist |
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| **Testing Facility:** | Dow Corning Corporation<br>Health and Environmental Sciences (HES)<br>2200 W. Salzburg Road<br>Auburn, Michigan 48611 |
| **Analysis Start Date:** | June 16, 2008 |
| **Analysis End Date:** | July 18, 2008 |

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# 1. APPROVAL SIGNATURES

Report Title: Functional Observational Battery (FOB) and Motor Activity Evaluation Results for a Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test for Dimethylsilanediol (DMSD), ZMAT 4065555 in Sprague-Dawley Rats via Oral Gavage

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## 2. OBJECTIVE

Functional Observational Battery (FOB) and evaluation of motor activity was performed to screen for neurotoxic effects of the test article on the designated toxicity groups.

## 3. EXPERIMENTAL

In the week prior to exposure (baseline) and during week four of exposure (treated), all animals of the toxicity groups were screened for neurotoxic effects using a Functional Observational Battery (FOB) and evaluation of motor activity. The FOB was conducted blind to treatment, under red lighting, and consisted of 2 types of data, ranked and continuous. The room temperature and relative humididty in the FOB room was continuously monitored during testing. The actual room temperature range was between (21.7°C - 24.4°C) and the humidity was maintained between (47%-56% RH). The first part of the FOB consisted of numerous hand-held and open field observations, which were ranked on a scale from 1-5 (none/low-exaggerated response). The second part of the FOB consisted of quantitative measurement of body temperature (rectal, Celsius), hindlimb/forelimb grip strength (grams), and landing foot splay (centimeters). Motor activity testing was conducted under reduced lighting (range 110-165 LUX) along with background noise (range 50-70 db white noise) to reduce the potential for distraction. The motor activity data (beam breaks or counts) were collected with a photobeam-type system and only ambulatory movement was assessed over 10, 8-minute intervals. To reduce any potential bias, the motor activity groups were counter-balanced across sessions and devices whenever possible (i.e., one animal from each group was tested in each session and in each device).

Pupil response was evaluated with a halogen penlite. An electronic solenoid valve (Skinner, Model #71315SN2GNJ1) was used to evaluate the response to sharp noise (measured at approximately 100 db). Rectal temperatures were measured using a YSI 4000 thermometer with a Model 402 probe. Grip strength was evaluated using a device manufactured for Dow Corning Corporation, which consisted of a horizontal coarse wire screen supported by four wheels attached to an electronic strain gauge (Chatillon, Model DFGS-R-ND with 10 kg load cell). Foot splay markings were measured with a digitizer (GTCO CalComp, Model Super L IV with a QuickRuler III measurement system). Motor Activity was measured with a Cage Rack Activity System (San Diego Instruments), which consisted of 7 photobeams spaced equally down the long sides of the rectangular units.

## 4. DATA ANALYSIS

The results were analyzed for statistical significance (see Appendix S of the main report) and reviewed for biological relevance (baseline and post-treatment group mean differences were reviewed for the treatment groups and compared to their respective control groups).

All data analysis was carried out using SAS version 9.1.3 [1]. Statistically significant probabilities were reported for p-values of < 0.05, <0.02, and < 0.01. Female animal # 5504 from the 50 mg/kg/day was excluded from statistical analysis due to being moved from the toxicology group to the reproductive group after baseline testing.

For Motor Activity, a repeated measurements ANOVA was performed to determine if a significant time by treatment group interaction exists. Repeated measurements ANOVAs were done using the time (baseline and post-treatment), interval, sex and treatment to look for interactions between the treatment, the time and sex to determine if analysis could be done with the sexes combined. See flow chart on the analysis of motor activity.

Categorical Functional Observational Battery (FOB) data was analyzed using the Jonckheere-Terpstra test[9]. The data was separated by sex and by time period (i.e., baseline and treated time periods). Therefore, baseline evaluations were not directly used as a variable in the statistical analysis of the treated data, but rather collected as reference to detect any pre-existing tendencies within the groups. This test is used to detect a shift in the categorical observations.

Measured continuous Functional Observational Battery (FOB) data was analyzed using a combination of ANCOVA with baseline evaluations used as the covariate and repeated measures ANOVA. A statistical check was initially performed to determine if there was a difference between the male and female data sets. The data were combined only when no statistical difference was found in an effort to increase statistical power. The baseline data was used as a variable in the analyses, however, the data in this report is only presented separated by sex.

## 5. DEVIATIONS

There were no deviations from the study protocol associated with the Neurotoxicity Evaluation for this study.

## 6. RESULTS AND DISCUSSION

### *6.1 FOB Ranked Tests*

The incidence of the various ranked scores recorded during the FOB testing was tabulated by group and can be found in Tables 1 and 2. Individual data are listed in Attachments A-D. There were no statistically significant or biologically relevant differences between the control and treatment groups in either sex at either of the time points for the FOB ranked tests: resistance to removal, palpebral closure, pupil reactivity, pupil size, lacrimation, salivation, muscle tone, extensor thrust, reactivity to handling, level of activity, response to touch, response to tail pinch, gait evaluation, urination, and categorical observations. However, for the males, there were statistically significant

differences across groups for the baseline response to sharp noise and treated defecation. There were no pair- wise differences between the control and any treated groups for the baseline response to sharp noise but the defecation in the 500 mg/kg/day group after treatment was statistically significantly higher than the control group, (Table 1, p. M12). Although statistically significant, these small departures from the control group were not considered biologically relevant. In addition, there are no other neurotoxicological signs affected, therefore, this increase is not considered to be evidence of a neurotoxic effect.

### *6.2 FOB Continuous Tests*

A summary of the FOB continuous tests can be found in Tables 3 and 4. The individual animal data are located in Attachments H-K.

*Body Temperature*
The ANCOVA with treatment by sex and treatment by covariate (baseline measurement) showed a significant treatment by sex interaction for the rectal temperature (p=0.0001)

The sexes separated ANCOVA showed no treatment effect. In conclusion, there were no differences between the treatment groups and their respective control groups for rectal temperature that were statistically significant or considered to be biologically relevant.

*Hindlimb Grip Strength*
The ANCOVA with treatment by sex and treatment by covariate (baseline measurement) showed a significant treatment by sex interaction for the hindlimb grip strength (p=0.0058)

The sexes separated ANCOVA showed no treatment effect. In conclusion, there were no differences between the treatment groups and their respective control groups for hindlimb grip strength that were statistically significant or considered to be biologically relevant.

*Forelimb Grip Strength*
The ANCOVA with treatment by sex and treatment by covariate (baseline measurement) did not show a significant treatment by sex interaction for the forelimb grip strength (p=0.4521).

Forelimb grip strength data was analyzed with the sexes combined using an Analysis of Covariance (ANCOVA). There were no differences between the treatment groups and control groups for forelimb grip strength that were statistically significant or considered to be biologically relevant.

*Landing Foot Splay*
The ANCOVA with treatment by sex and treatment by covariate (baseline measurement) showed a significant treatment by sex interaction for the landing foot splay (p=0.0396).

The sexes separated ANCOVA showed no treatment effect. In conclusion, there were no differences between the treatment groups and their respective control groups for landing foot splay that were statistically significant or considered to be biologically relevant.

### *6.3 Motor Activity*

A summary of the motor activity data can be found in Tables 5 and 6. Individual animal data are located in Attachments L-O. Total counts and habituation (decrease in exploratory behavior over time) were analyzed statistically for differences compared to control. The statistical analysis on the combined untransformed data determined that the data was homogeneous and normally distributed, therefore, no transformation of the data was necessary. The baseline data was used as a variable in the analyses.

*Total Counts*
Total count data was analyzed with the sexes combined and using a Repeated Measures Analysis of Variance (RMANOVA). There were no statistically significant or biologically relevant differences between the treatment groups and the control group for motor activity.

*Habituation*
Interval data was analyzed with the sexes combined using a Repeated Measures Analysis of Variance (RMANOVA). There were no statistically significant or biologically relevant differences noted between the treatment groups and the control group for motor activity habituation for either male or female.

## 7. CONCLUSIONS

Based on the evaluations performed, as described within the context of this contributing scientist report, there were no treatment-related effects associated with Dimethylsilanediol exposure on rat neurobiological function.

## 8. REFERENCES

1. OECD Guideline for Testing of Chemicals, "Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test", No. 422, Adopted March 22, 1996.

2. EPA Health Effects Test Guidelines, "OPPTS 870.6200 Neurotoxicity Screening Battery", August 1998.

## Table 1 Summary of FOB Ranked/Categorical Incidence – Male Rats

| | Baseline | | | | Treated | | | |
|---|---|---|---|---|---|---|---|---|
| **Dose Group** | **1** | **2** | **3** | **4** | **1** | **2** | **3** | **4** |
| Number of Animals Examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Resistance to Removal** | | | | | | | | |
| (3) Moderate; actively avoids capture but is not aggressive | 10 | 10 | 10 | 8 | 10 | 10 | 10 | 10 |
| (4) Pronounced; actively avoids capture and/or is mildly aggressive | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| (5) Exaggerated; very difficult to capture and is very aggressive (i.e. tries to bite) | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| **Palpebral Closure** | | | | | | | | |
| (3) Open | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Pupil Reactivity** | | | | | | | | |
| (3) dilated, briskly reactive pupil | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Pupil Size** | | | | | | | | |
| (3) Normal pupil size | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Lacrimation** | | | | | | | | |
| (3) Glistening cornea | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Salivation** | | | | | | | | |
| (3) glistening oral cavity/lips, no wetness | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Muscle Tone** | | | | | | | | |
| (3) moderate; animal is neither very relaxed nor tense | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day

## Table 1 Summary of FOB Ranked/Categorical Incidence – Male Rats (continued)

| | Baseline | | | | Treated | | | |
|---|---|---|---|---|---|---|---|---|
| **Dose Group** | **1** | **2** | **3** | **4** | **1** | **2** | **3** | **4** |
| Number of Animals Examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Extensor Thrust** | | | | | | | | |
| (3) moderate; clearly detectable | 10 | 10 | 10 | 10 | 9 | 10 | 10 | 9 |
| (4) Pronounced; pushes vigorously | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| **Reactivity to Handling** | | | | | | | | |
| (3) moderate struggling with little or no vocalization | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Level of Activity** | | | | | | | | |
| (2) minimal, inactive more than 50% of the time | 0 | 1 | 0 | 1 | 3 | 4 | 3 | 5 |
| (3) moderate, inactive less than 50% of the time | 10 | 9 | 10 | 9 | 7 | 6 | 7 | 5 |
| **Response to Noise** | * | | | | | | | |
| (3) moderate; clear movement of the head, neck, ears and possibly front shoulders/upper body | 10 | 10 | 8 | 7 | 7 | 9 | 8 | 9 |
| (4) pronounced; clear movement of head, neck and ears, plus clear movement of whole body | 0 | 0 | 2 | 3 | 3 | 1 | 2 | 0 |
| (5) exaggerated; whole body response to stimulus, more intense than "pronounced"; includes whole body | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| **Response to Touch** | | | | | | | | |
| (3) moderate; spontaneously lifts tail when touched | 10 | 9 | 10 | 8 | 10 | 10 | 10 | 9 |
| (4) Pronounced; spontaneously lifts tail and acts startled | 0 | 1 | 0 | 2 | 0 | 0 | 0 | 1 |

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day
*Asterisks indicate a significant difference across treatment groups (in the control column) or between control and a treatment group with p-values of * < 0.05, ** < 0.02 or *** < 0.01.

## Table 1 Summary of FOB Ranked/Categorical Incidence – Male Rats (continued)

| | Baseline | | | | Treated | | | |
|---|---|---|---|---|---|---|---|---|
| **Dose Group** | **1** | **2** | **3** | **4** | **1** | **2** | **3** | **4** |
| Number of Animals Examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Response to Tail Pinch** | | | | | | | | |
| (2) minimal; animal flinches and may vocalize | 1 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| (3) moderate; animal flinches, moves rapidly and/or vocalizes | 9 | 10 | 10 | 10 | 8 | 10 | 10 | 10 |
| **Gait Evaluation** | | | | | | | | |
| (1) smooth and coordinated gait | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Urination** | | | | | | | | |
| (1) no drops of urine | 3 | 1 | 4 | 2 | 1 | 1 | 0 | 1 |
| (2) minimal; a few (1-4) small drops or a small pool (~1 cm) | 3 | 4 | 3 | 5 | 3 | 0 | 0 | 2 |
| (3) moderate; a few (1-4) small pools or a moderate pool (2-3 cm) | 0 | 2 | 2 | 0 | 1 | 1 | 4 | 2 |
| (4) pronounced; a few (1-4) moderate pools or a large pool (4-5 cm) | 1 | 1 | 0 | 0 | 3 | 1 | 2 | 2 |
| (5) Exaggerated; >4 moderate pools or single pool >5 cm. | 3 | 2 | 1 | 3 | 2 | 7 | 4 | 3 |

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day

## Table 1 Summary of FOB Ranked/Categorical Incidence – Male Rats (continued)

| | Baseline | | | | Treated | | | |
|---|---|---|---|---|---|---|---|---|
| Dose Group | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Number of Animals Examined | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Defecation** | | | | | *** | | | * |
| (1) no pellets voided | 5 | 7 | 5 | 3 | 4 | 3 | 1 | 1 |
| (2) minimal; 1 or 2 pellets voided | 4 | 1 | 3 | 5 | 3 | 4 | 5 | 1 |
| (3) moderate ; 3 pellets voided | 0 | 1 | 2 | 1 | 1 | 1 | 3 | 2 |
| (4) pronounced; 4 pellets voided | 0 | 1 | 0 | 0 | 2 | 1 | 0 | 3 |
| (5) Exaggerated; 5 or more pellets voided | 1 | 0 | 0 | 1 | 0 | 1 | 1 | 3 |
| **Categorical Observations** | | | | | | | | |
| No Abnormalities Detected | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 8 |
| Soiling Perineal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day
*Asterisks indicate a significant difference across treatment groups (in the control column) or between control and a treatment group with p-values of * < 0.05, ** < 0.02 or *** < 0.01.

## Table 2 Summary of FOB Ranked/Categorical Incidence – Female Rats

| | Baseline | | | | Treated | | | |
|---|---|---|---|---|---|---|---|---|
| Dose Group | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Number of Animals Examined | 10 | 9^ | 10 | 10 | 10 | 9 | 10 | 10 |
| **Resistance to Removal** | | | | | | | | |
| (2) Minimally avoids capture but is not aggressive | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| (3) Moderate; actively avoids capture but is not aggressive | 10 | 7 | 10 | 10 | 9 | 9 | 10 | 10 |
| (4) Pronounced; actively avoids capture and/or is mildly aggressive | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Palpebral Closure** | | | | | | | | |
| (3) Open | 10 | 9 | 10 | 10 | 10 | 9 | 10 | 10 |
| **Pupil Reactivity** | | | | | | | | |
| (3) dilated, briskly reactive pupil | 10 | 9 | 10 | 10 | 10 | 9 | 10 | 10 |
| **Pupil Size** | | | | | | | | |
| (3) Normal pupil size | 10 | 9 | 10 | 10 | 10 | 9 | 10 | 10 |
| **Lacrimation** | | | | | | | | |
| (3) Glistening cornea | 10 | 9 | 10 | 10 | 10 | 9 | 10 | 10 |
| **Salivation** | | | | | | | | |
| (3) glistening oral cavity/lips, no wetness | 10 | 9 | 10 | 10 | 10 | 9 | 10 | 10 |

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day
^ Animal excluded from statistical analysis due to being moved from the toxicology group to the reproductive group after baseline testing.

**Table 2 Summary of FOB Ranked/Categorical Incidence – Female Rats (continued)**

| | Baseline | | | | Treated | | | |
|---|---|---|---|---|---|---|---|---|
| **Dose Group** | **1** | **2** | **3** | **4** | **1** | **2** | **3** | **4** |
| Number of Animals Examined | 10 | 9^A | 10 | 10 | 10 | 9 | 10 | 10 |
| **Muscle Tone** | | | | | | | | |
| (3) moderate; animal is neither very relaxed nor tense | 10 | 9 | 10 | 10 | 10 | 9 | 10 | 10 |
| **Extensor Thrust** | | | | | | | | |
| (3) moderate; clearly detectable | 10 | 9 | 10 | 10 | 10 | 9 | 10 | 10 |
| **Reactivity to Handling** | | | | | | | | |
| (3) moderate struggling with little or no vocalization | 9 | 8 | 10 | 10 | 10 | 9 | 10 | 10 |
| (4) pronounced struggling, animal may vocalize | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Level of Activity** | | | | | | | | |
| (2) minimal, inactive more than 50% of the time | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| (3) moderate, inactive less than 50% of the time | 10 | 9 | 10 | 10 | 9 | 8 | 10 | 10 |
| (4) pronounced; leaves circle, occasional inactivity | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day
^A Animal excluded from statistical analysis due to being moved from the toxicology group to the reproductive group after baseline testing

## Table 2 Summary of FOB Ranked/Categorical Incidence – Female Rats (continued)

| | Baseline | | | | Treated | | | |
|---|---|---|---|---|---|---|---|---|
| Dose Group | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Number of Animals Examined | 10 | 9[A] | 10 | 10 | 10 | 9 | 10 | 10 |
| **Response to Noise** | | | | | | | | |
| (3) moderate; clear movement of the head, neck, ears and possibly front shoulders/upper body | 8 | 8 | 9 | 8 | 6 | 4 | 8 | 6 |
| (4) pronounced; clear movement of head, neck and ears, plus clear movement of whole body | 2 | 1 | 1 | 2 | 4 | 5 | 2 | 3 |
| (5) exaggerated; whole body response to stimulus, more intense than "pronounced"; includes whole body | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| **Response to Touch** | | | | | | | | |
| (3) moderate; spontaneously lifts tail when touched | 10 | 8 | 9 | 10 | 10 | 9 | 10 | 10 |
| (4) Pronounced; spontaneously lifts tail and acts startled | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 |
| **Response to Tail Pinch** | | | | | | | | |
| (2) minimal; animal flinches and may vocalize | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| (3) moderate; animal flinches, moves rapidly and/or vocalizes | 10 | 9 | 9 | 10 | 10 | 9 | 10 | 10 |
| **Gait Evaluation** | | | | | | | | |
| (1) smooth and coordinated gait | 10 | 9 | 10 | 10 | 10 | 9 | 10 | 10 |

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day
[A] Animal excluded from statistical analysis due to being moved from the toxicology group to the reproductive group after baseline testing.

## Table 2 Summary of FOB Ranked/Categorical Incidence – Female Rats (continued)

| | Baseline | | | | Treated | | | |
|---|---|---|---|---|---|---|---|---|
| **Dose Group** | **1** | **2** | **3** | **4** | **1** | **2** | **3** | **4** |
| Number of Animals Examined | 10 | 9[A] | 10 | 10 | 10 | 9 | 10 | 10 |
| **Urination** | | | | | | | | |
| (1) no drops of urine | 5 | 2 | 1 | 2 | 1 | 2 | 4 | 1 |
| (2) minimal; a few (1-4) small drops or a small pool (~1 cm) | 4 | 6 | 6 | 6 | 4 | 4 | 4 | 7 |
| (3) moderate; a few (1-4) small pools or a moderate pool (2-3 cm) | 0 | 0 | 3 | 2 | 4 | 3 | 1 | 1 |
| (4) pronounced; a few (1-4) moderate pools or a large pool (4-5 cm) | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| (5) Exaggerated; >4 moderate pools or single pool >5 cm. | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 0 |
| **Defecation** | | | | | | | | |
| (1) no pellets voided | 8 | 9 | 9 | 9 | 7 | 6 | 8 | 6 |
| (2) minimal; 1 or 2 pellets voided | 2 | 0 | 0 | 1 | 2 | 0 | 2 | 1 |
| (3) moderate ; 3 pellets voided | 0 | 0 | 0 | 0 | 1 | 2 | 0 | 1 |
| (4) pronounced; 4 pellets voided | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| (5) Exaggerated; 5 or more pellets voided | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 1 |
| **Categorical Observations** | | | | | | | | |
| No Abnormalities Detected | 10 | 10 | 10 | 10 | 10 | 9 | 9 | 10 |
| Soiling Abdominal, Soiling Perineal | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day
[A] Animal excluded from statistical analysis due to being moved from the toxicology group to the reproductive group after baseline testing

## Table 3 Summary of FOB Continuous Data – Male Rats

| Group Sex | | Baseline | | | | Treated | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Rectal Temperature (°C) | Hindlimb Grip Strength (g) | Forelimb Grip Strength (g) | Landing Foot Splay (cm) | Rectal Temperature (°C) | Hindlimb Grip Strength (g) | Forelimb Grip Strength (g) | Landing Foot Splay (cm) |
| 1m | Mean | 37.5 | 814.5 | 818.5 | 13.4 | 38.0 | 1249.5 | 1077.0 | 13.2 |
| | S.D. | 0.5 | 145.8 | 143.0 | 1.44 | 0.5 | 126.7 | 258.8 | 2.2 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| 2m | Mean | 37.6 | 750.9 | 809.3 | 13.2 | 38.0 | 1222.0 | 1111.7 | 11.9 |
| | S.D. | 0.5 | 114.9 | 141.7 | 1.3 | 0.4 | 150.8 | 188.8 | 1.5 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| 3m | Mean | 37.7 | 704.8 | 745.2 | 13.4 | 37.9 | 1235.5 | 1022.2 | 11.8 |
| | S.D. | 0.3 | 130.2 | 90.2 | 1.7 | 0.2 | 165.5 | 268.9 | 1.5 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| 4m | Mean | 37.7 | 716.4 | 813.5 | 12.0 | 37.8 | 1065.2 | 992.5 | 12.0 |
| | S.D. | 0.4 | 111.5 | 166.4 | 2.0 | 0.4 | 180.2 | 163.5 | 1.5 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day

## Table 4 Summary of FOB Continuous Data – Female Rats

| Group Sex | | Baseline | | | | Treated | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Rectal Temperature (°C) | Hindlimb Grip Strength (g) | Forelimb Grip Strength (g) | Landing Foot Splay (cm) | Rectal Temperature (°C) | Hindlimb Grip Strength (g) | Forelimb Grip Strength (g) | Landing Foot Splay (cm) |
| 1f | Mean | 38.1 | 693.2 | 721.8 | 10.8 | 38.2 | 1005.5 | 866.0 | 9.8 |
| | S.D. | 0.6 | 119.1 | 69.6 | 1.0 | 0.4 | 138.2 | 170.6 | 1.5 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| 2f | Mean | 38.0 | 649.4 | 737.2 | 10.6 | 38.4 | 1019.3 | 975.9 | 11.4 |
| | S.D. | 0.3 | 101.6 | 91.7 | 2.2 | 0.4 | 105.7 | 145.6 | 2.0 |
| | N* | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| 3f | Mean | 37.9 | 681.5 | 721.3 | 10.9 | 38.4 | 1108.3 | 992.5 | 10.1 |
| | S.D. | 0.4 | 107.7 | 86.4 | 1.8 | 0.3 | 193.1 | 237.3 | 1.3 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| 4f | Mean | 38.0 | 719.0 | 743.7 | 10.9 | 38.5 | 985.7 | 990.2 | 10.5 |
| | S.D. | 0.4 | 163.2 | 81.0 | 1.9 | 0.3 | 225.6 | 178.3 | 1.9 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day
* Animal excluded from statistical analysis due to being moved from the toxicology group to the reproductive group after baseline testing.

Dow Corning Corporation
HES Study Number: 10872-102
Appendix M

## Table 5 Motor Activity Summary – Male Rats

| Interval | Group/Sex | Baseline 1m | Baseline 2m | Baseline 3m | Baseline 4m | Treated 1m | Treated 2m | Treated 3m | Treated 4m |
|---|---|---|---|---|---|---|---|---|---|
| (8 minutes) | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| 1 | Mean | 238 | 259 | 212 | 221 | 225 | 248 | 191 | 229 |
| | S.D. | 39 | 58 | 33 | 48 | 46 | 83 | 44 | 31 |
| 2 | Mean | 174 | 218 | 179 | 156 | 173 | 172 | 140 | 141 |
| | S.D. | 54 | 55 | 46 | 49 | 57 | 65 | 56 | 34 |
| 3 | Mean | 141 | 151 | 131 | 115 | 91 | 134 | 102 | 100 |
| | S.D. | 58 | 68 | 62 | 77 | 26 | 59 | 35 | 40 |
| 4 | Mean | 109 | 132 | 112 | 80 | 50 | 54 | 66 | 53 |
| | S.D. | 53 | 83 | 80 | 81 | 32 | 49 | 40 | 27 |
| 5 | Mean | 98 | 85 | 58 | 35 | 40 | 65 | 52 | 48 |
| | S.D. | 73 | 83 | 54 | 52 | 29 | 75 | 40 | 37 |
| 6 | Mean | 69 | 32 | 55 | 23 | 49 | 51 | 45 | 45 |
| | S.D. | 67 | 46 | 58 | 40 | 41 | 51 | 37 | 55 |
| 7 | Mean | 35 | 27 | 14 | 19 | 51 | 44 | 43 | 19 |
| | S.D. | 38 | 45 | 23 | 39 | 49 | 30 | 37 | 27 |
| 8 | Mean | 13 | 3 | 39 | 0 | 31 | 37 | 30 | 9 |
| | S.D. | 31 | 9 | 48 | 1 | 34 | 35 | 35 | 21 |
| 9 | Mean | 15 | 3 | 34 | 1 | 26 | 45 | 22 | 6 |
| | S.D. | 30 | 8 | 51 | 1 | 39 | 38 | 39 | 8 |
| 10 | Mean | 14 | 1 | 6 | 2 | 31 | 23 | 26 | 23 |
| | S.D. | 44 | 2 | 15 | 5 | 34 | 31 | 34 | 31 |
| Total | Mean | 906 | 911 | 840 | 651 | 766 | 873 | 716 | 673 |
| | S.D. | 290 | 348 | 275 | 286 | 222 | 323 | 210 | 153 |

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day

## Table 6 Motor Activity Summary – Female Rats

| Interval | Group/Sex | Baseline 1f | 2f | 3f | 4f | Treated 1f | 2f | 3f | 4f |
|---|---|---|---|---|---|---|---|---|---|
| (8 minutes) | N* | 10 | 9 | 10 | 10 | 10 | 9 | 10 | 10 |
| 1 | Mean | 252 | 254 | 268 | 232 | 246 | 203 | 211 | 213 |
| | S.D. | 46 | 44 | 40 | 25 | 33 | 44 | 39 | 34 |
| 2 | Mean | 191 | 172 | 189 | 181 | 191 | 166 | 162 | 154 |
| | S.D. | 41 | 30 | 46 | 22 | 62 | 44 | 42 | 30 |
| 3 | Mean | 156 | 105 | 131 | 137 | 150 | 122 | 146 | 127 |
| | S.D. | 58 | 70 | 34 | 47 | 63 | 43 | 44 | 40 |
| 4 | Mean | 120 | 75 | 110 | 84 | 116 | 101 | 96 | 98 |
| | S.D. | 60 | 54 | 29 | 54 | 73 | 70 | 49 | 43 |
| 5 | Mean | 115 | 53 | 80 | 66 | 126 | 89 | 98 | 75 |
| | S.D. | 75 | 53 | 65 | 54 | 78 | 54 | 61 | 40 |
| 6 | Mean | 100 | 44 | 37 | 47 | 120 | 64 | 72 | 70 |
| | S.D. | 65 | 44 | 72 | 58 | 115 | 44 | 51 | 35 |
| 7 | Mean | 116 | 37 | 43 | 38 | 97 | 51 | 88 | 77 |
| | S.D. | 83 | 42 | 67 | 48 | 63 | 58 | 45 | 42 |
| 8 | Mean | 91 | 8 | 33 | 29 | 109 | 53 | 51 | 59 |
| | S.D. | 50 | 21 | 38 | 47 | 64 | 52 | 35 | 37 |
| 9 | Mean | 66 | 17 | 65 | 19 | 83 | 52 | 62 | 74 |
| | S.D. | 78 | 33 | 90 | 31 | 46 | 41 | 56 | 45 |
| 10 | Mean | 51 | 2 | 57 | 8 | 93 | 70 | 49 | 50 |
| | S.D. | 58 | 5 | 95 | 21 | 61 | 47 | 42 | 14 |
| Total | Mean | 1257 | 766 | 1013 | 840 | 1330 | 971 | 1034 | 996 |
| | S.D. | 468 | 269 | 402 | 273 | 457 | 338 | 303 | 160 |

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day
* Animal excluded from statistical analysis due to being moved from the toxicology group to the reproductive group after baseline testing.

## Attachment A Individual FOB Ranked – Male Rats (Baseline)

| Group/Sex | Animal # | Resistance to Removal | Palpebral Closure | Pupil Reactivity | Pupil Size | Lacrimation | Salivation | Muscle Tone | Extensor Thrust | Reactivity to handling | Level of Activity | Response to Noise | Response to Touch | Response to Tail Pinch | Gait Evaluation | Urination | Defecation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1m | 5484 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 2 |
| | 5485 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 5 | 1 |
| | 5486 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 1 | 2 |
| | 5487 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 2 |
| | 5488 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 2 | 1 | 4 | 5 |
| | 5489 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 5 | 1 |
| | 5490 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 1 | 1 |
| | 5491 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 1 | 2 |
| | 5492 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 5 | 1 |
| | 5493 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 1 |
| 2m | 5514 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 4 |
| | 5515 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 5 | 1 |
| | 5516 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 4 | 3 |
| | 5517 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 5 | 1 |
| | 5518 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 | 1 | 2 | 2 |
| | 5519 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 1 |
| | 5520 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 2 | 3 | 3 | 3 | 1 | 1 | 1 |
| | 5521 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 1 |
| | 5522 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 3 | 1 |
| | 5523 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 3 | 1 |

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day

## Attachment A Individual FOB Ranked – Male Rats (Baseline) Continued

| Group/Sex | Animal # | Resistance to Removal | Palpebral Closure | Pupil Reactivity | Pupil Size | Lacrimation | Salivation | Muscle Tone | Extensor Thrust | Reactivity to handling | Level of Activity | Response to Noise | Response to Touch | Response to Tail Pinch | Gait Evaluation | Urination | Defecation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3m | 5544 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 2 |
| | 5545 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 1 |
| | 5546 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 1 | 3 |
| | 5547 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 | 3 | 1 | 5 | 3 |
| | 5548 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 1 | 2 |
| | 5549 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 3 | 2 |
| | 5550 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 1 |
| | 5551 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 | 3 | 1 | 1 | 1 |
| | 5552 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 1 | 1 |
| | 5553 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 3 | 1 |
| 4m | 5574 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 | 1 | 2 | 2 |
| | 5575 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 1 | 1 |
| | 5576 | 4 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 5 | 5 |
| | 5577 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 2 | 3 | 3 | 3 | 1 | 2 | 2 |
| | 5578 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 5 | 1 |
| | 5579 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 | 3 | 1 | 2 | 1 |
| | 5580 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 2 |
| | 5581 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 | 3 | 1 | 2 | 2 |
| | 5582 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 5 | 3 |
| | 5583 | 5 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 4 | 3 | 1 | 1 | 2 |

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day

## Attachment B Individual FOB Ranked – Male Rats (Treated)

| Group/Sex | Animal # | Resistance to Removal | Palpebral Closure | Pupil Reactivity | Pupil Size | Lacrimation | Salivation | Muscle Tone | Extensor Thrust | Reactivity to handling | Level of Activity | Response to Noise | Response to Touch | Response to Tail Pinch | Gait Evaluation | Urination | Defecation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1m | 5484 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 | 3 | 1 | 1 | 2 |
| | 5485 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 5 | 1 |
| | 5486 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 1 |
| | 5487 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 | 3 | 3 | 3 | 3 | 1 | 3 | 4 |
| | 5488 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 2 | 4 | 3 | 3 | 1 | 5 | 3 |
| | 5489 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 2 | 1 | 4 | 2 |
| | 5490 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 2 | 4 | 3 | 2 | 1 | 2 | 1 |
| | 5491 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 1 |
| | 5492 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 4 | 2 |
| | 5493 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 2 | 3 | 3 | 3 | 1 | 4 | 4 |
| 2m | 5514 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 2 | 3 | 3 | 3 | 1 | 5 | 2 |
| | 5515 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 5 | 1 |
| | 5516 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 3 | 1 |
| | 5517 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 2 | 3 | 3 | 3 | 1 | 5 | 4 |
| | 5518 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 5 | 2 |
| | 5519 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 2 | 3 | 3 | 3 | 1 | 4 | 5 |
| | 5520 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 2 | 4 | 3 | 3 | 1 | 5 | 1 |
| | 5521 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 5 | 3 |
| | 5522 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 5 | 2 |
| | 5523 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 1 | 2 |

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day

## Attachment B Individual FOB Ranked – Male Rats (Treated) Continued

| Group/Sex | Animal # | Resistance to Removal | Palpebral Closure | Pupil Reactivity | Pupil Size | Lacrimation | Salivation | Muscle Tone | Extensor Thrust | Reactivity to handling | Level of Activity | Response to Noise | Response to Touch | Response to Tail Pinch | Gait Evaluation | Urination | Defecation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3m | 5544 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 2 | 3 | 3 | 3 | 1 | 3 | 3 |
| | 5545 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 5 | 3 |
| | 5546 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 | 3 | 1 | 5 | 2 |
| | 5547 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 5 | 5 |
| | 5548 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 5 | 2 |
| | 5549 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 4 | 2 |
| | 5550 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 2 | 3 | 3 | 3 | 1 | 3 | 1 |
| | 5551 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 2 | 4 | 3 | 3 | 1 | 3 | 2 |
| | 5552 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 4 | 2 |
| | 5553 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 3 | 3 |
| 4m | 5574 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 | 3 | 3 | 3 | 3 | 1 | 1 | 3 |
| | 5575 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 5 | 5 |
| | 5576 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 2 | 3 | 3 | 3 | 1 | 4 | 3 |
| | 5577 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 2 | 3 | 3 | 3 | 1 | 5 | 5 |
| | 5578 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 1 |
| | 5579 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 2 | 3 | 3 | 3 | 1 | 5 | 2 |
| | 5580 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 2 | 3 | 3 | 3 | 1 | 3 | 4 |
| | 5581 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 2 | 3 | 3 | 3 | 1 | 3 | 4 |
| | 5582 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 4 | 5 |
| | 5583 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 5 | 4 | 3 | 1 | 2 | 4 |

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day

## Attachment C Individual FOB Ranked – Female Rats (Baseline)

| Group/Ses | Animal # | Resistance to Removal | Palpebral Closure | Pupil Reactivity | Pupil Size | Lacrimation | Salivation | Muscle Tone | Extensor Thrust | Reactivity to handling | Level of Activity | Response to Noise | Response to Touch | Response to Tail Pinch | Gait Evaluation | Urination | Defecation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1f | 5474 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 1 |
| | 5475 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 | 3 | 1 | 1 | 1 |
| | 5476 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 | 3 | 3 | 3 | 1 | 2 | 2 |
| | 5477 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 1 | 1 |
| | 5478 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 | 3 | 1 | 2 | 1 |
| | 5479 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 1 |
| | 5480 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 1 | 1 |
| | 5481 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 1 | 2 |
| | 5482 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 1 | 1 |
| | 5483 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 5 | 1 |
| 2f | 5504* | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 1 |
| | 5505 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 | 1 | 2 | 1 |
| | 5506 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 1 | 1 |
| | 5507 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 1 |
| | 5508 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 | 3 | 1 | 2 | 1 |
| | 5509 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 1 |
| | 5510 | 4 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 | 3 | 3 | 3 | 1 | 1 | 1 |
| | 5511 | 4 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 1 |
| | 5512 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 5 | 1 |
| | 5513 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 1 |

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day
* Animal excluded from statistical analysis due to being moved from the toxicology group to the reproductive group after baseline testing.

## Attachment C Individual FOB Ranked – Female Rats (Baseline) Continued

| Group/Sex | Animal # | Resistance to Removal | Palpebral Closure | Pupil Reactivity | Pupil Size | Lacrimation | Salivation | Muscle Tone | Extensor Thrust | Reactivity to handling | Level of Activity | Response to Noise | Response to Touch | Response to Tail Pinch | Gait Evaluation | Urination | Defecation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3f | 5534 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 1 |
| | 5535 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 3 | 1 |
| | 5536 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 4 | 3 | 1 | 2 | 1 |
| | 5537 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 3 | 1 |
| | 5538 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 1 |
| | 5539 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 1 |
| | 5540 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 5 |
| | 5541 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 1 | 1 |
| | 5542 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 1 |
| | 5543 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 2 | 1 | 3 | 1 |
| 4f | 5564 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 1 |
| | 5565 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 | 3 | 1 | 2 | 1 |
| | 5566 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 1 | 2 |
| | 5567 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 | 3 | 1 | 3 | 1 |
| | 5568 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 3 | 1 |
| | 5569 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 1 |
| | 5570 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 1 |
| | 5571 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 1 |
| | 5572 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 1 | 1 |
| | 5573 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 1 |

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day

## Attachment D Individual FOB Ranked – Female Rats (Treated)

| Group/Sex | Animal # | Resistance to Removal | Palpebral Closure | Pupil Reactivity | Pupil Size | Lacrimation | Salivation | Muscle Tone | Extensor Thrust | Reactivity to handling | Level of Activity | Response to Noise | Response to Touch | Response to Tail Pinch | Gait Evaluation | Urination | Defecation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1f | 5474 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 | 3 | 1 | 2 | 1 |
| | 5475 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 | 3 | 1 | 1 | 1 |
| | 5476 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 4 | 2 |
| | 5477 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 1 |
| | 5478 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 3 | 3 |
| | 5479 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 | 3 | 1 | 2 | 1 |
| | 5480 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 2 | 3 | 3 | 3 | 1 | 2 | 2 |
| | 5481 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 3 | 1 |
| | 5482 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 3 | 1 |
| | 5483 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 | 3 | 1 | 3 | 1 |
| 2f | 5505 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 | 3 | 1 | 3 | 1 |
| | 5506 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 | 3 | 1 | 1 | 1 |
| | 5507 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 1 |
| | 5508 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 | 3 | 1 | 2 | 1 |
| | 5509 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 | 3 | 3 | 1 | 1 | 1 |
| | 5510 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 | 3 | 1 | 2 | 5 |
| | 5511 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 3 | 3 |
| | 5512 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 1 |
| | 5513 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 | 3 | 1 | 3 | 3 |

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day

## Attachment D Individual FOB Ranked - Female Rats (Treated) Continued

| Group/Sex | Animal # | Resistance to Removal | Palpebral Closure | Pupil Reactivity | Pupil Size | Lacrimation | Salivation | Muscle Tone | Extensor Thrust | Reactivity to handling | Level of Activity | Response to Noise | Response to Touch | Response to Tail Pinch | Gait Evaluation | Urination | Defecation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3f | 5534 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 1 |
| | 5535 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 | 3 | 1 | 1 | 1 |
| | 5536 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 1 |
| | 5537 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 1 |
| | 5538 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 | 3 | 1 | 5 | 2 |
| | 5539 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 1 | 1 |
| | 5540 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 1 |
| | 5541 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 1 | 1 |
| | 5542 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 1 | 1 |
| | 5543 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 3 | 2 |
| 4f | 5564 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 1 |
| | 5565 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 1 |
| | 5566 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 | 3 | 1 | 2 | 4 |
| | 5567 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 3 |
| | 5568 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 3 | 1 |
| | 5569 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 | 3 | 1 | 4 | 1 |
| | 5570 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 2 |
| | 5571 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 | 3 | 1 | 2 | 5 |
| | 5572 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 1 |
| | 5573 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 5 | 3 | 3 | 1 | 1 | 1 |

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day

## Attachment E FOB Ranked/Categorical Observations Definitions

**Definitions:**

Resistance to Removal:
1 = no resistance to capture and removal
2 = minimally avoids capture but is not aggressive
3 = moderate; actively avoids capture but is not aggressive
4 = pronounced; actively avoids capture and/or is mildly aggressive
5 = exaggerated; very difficult to capture and is very aggressive (i.e. tries to bite)

Pupil reactivity :
1 = dilated, nonreactive pupil
2 = dilated, slowly reactive pupil
3 = dilated, briskly reactive pupil
4 = constricted, cannot assess

Lacrimation:
1 = very dry appearance of cornea
2 = slightly dry appearance of cornea
3 = glistening cornea
4 = slight periocular wetness
5 = extensive periocular wetness

Muscle tone:
1 = scored as none but defined as limp
2 = slight; very relaxed, "soft"
3 = moderate; animal is neither very relaxed nor tense
4 = pronounced; animal feels slightly rigid or tense
5 = exaggerated; very rigid or stiff

Reactivity to handling:
1 = none, no struggling
2 = minimal struggling
3 = moderate struggling with little or no vocalization
4 = pronounced struggling, animal may vocalize
5 = exaggerated; aggressive escape behavior, tries to bite observer and usually vocalizes

Palpebral closure:
1 = closed
2 = 50% closed
3 = open
4 = protruding eyes

Pupil size :
1 = decreased pupil size (completely constricted)
2 = decreased pupil size (slightly constricted)
3 = normal pupil size
4 = increased pupil size (slightly dilated)
5 = increased pupil size (completely dilated)

Salivation:
1 = extensive oral dryness
2 = slight oral dryness
3 = gistening oral cavity/lips, no wetness
4 = slight perioral wetness
5 = extensive perioral wetness or drop(s) of fluid in or around mouth

Extensor-thrust response:
1 = no extensor thrust response
2 = slight; barely detectable response
3 = moderate; clearly detectable
4 = pronounced; pushes vigorously
5 = exaggerated; extreme thrust response

Level of activity :
1 = none, rat doesn't leave the center circle (20 cm dia.)
2 = minimal; inactive more than 50% of the time
3 = moderate; inactive less than 50% of the time
4 = pronounced; leaves circle, occasional inactivity.
5 = exaggerated; leaves circle, never inactive.

## Attachment E FOB Ranked/Categorical Observations Definitions - Continued

Responsiveness to sharp noise:
1 = none, no response to click
2 = minimal; only the ears and/or head moves
3 = moderate; clear movement of the head, neck, ears and possibly front shoulders/upper body
4 = pronounced; clear movement of head, neck and ears, plus clear movement of whole body.
5 = exaggerated; whole body response to stimulus, more intense than "pronounced", includes whole body going airborne.

Responsiveness to touch:
1 = no response to touch
2 = slight; does not spontaneously lift tail; but briefly holds tail in air when manually lifted
3 = moderate; spontaneously lifts tail when touched
4 = pronouneed; spontaneously lifts tail and acts startled
5 = exaggerated; turns towards finger in an attack response

Responsiveness to tail pinch :
1 = none; no response to pinch
2 = minimal; animal flinches and may vocalize slightly
3 = moderate; animal flinches, moves rapidly and/or vocalizes
4 = pronounced; animal moves vigorously in opposite direction of source of stimulation and vocalizes repeatedly and/or bends towards the tail and vocalizes
5 = exaggerated response to pinch; same as "pronounced", but includes an attempt to attack the source of the stimulation

Gait evaluation.
1 = smooth and coordinated gait
2 = slight knuckling of the paws and/or slight tendency to stumble
3 = moderate; clear knuckling and stumbling; incoordination
4 = pronounced; to include but not limited to: poor coordination, falling, and/or clear and repetitive knuckling of paws, and/or dragging of one or more limbs
5 = exaggerated; animal is unable to walk

Urination:
1 = no drops of urine
2 = minimal; a few ( 1-4) small drops or a small pool ( ~1 cm)
3 = moderate; a few (1-4) small pools or a moderate pool (2-3 cm)
4 = pronounced; a few (1-4) moderate pools or a large pool (4-5 cm)
5 = exaggerated; >4 moderate pools or a single pool >5 cm

Defecation:
1 = no pellets voided
2 = minimal; 1 or 2 pellets voided
3 = moderate; 3 pellets voided
4 = pronounced; 4 pellets voided
5 = exaggerated; 5 or more pellets voided

**Categoricals:**

Positive Observations made at any time regarding the following categories:

| | | |
|---|---|---|
| Behavior | Urine or Feces | Other abnormalities |
| Skin/fur/mucous membranes | Soiling | |
| Respiration | Posture | |
| Muscle | Eyes | |

# Attachment F Individual FOB Categorical Observations – Males

| | | | | Day numbers relative to Start Date | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Group | Sex | Animal | Clinical Sign | -7 | -6 | -5 | -4 | -3 | 22 | 23 | 24 | 25 | 26 |
| 1 | m | 5484 | No Abnormalities Detected | . | X | . | . | . | . | X | . | . | . |
| | | 5485 | No Abnormalities Detected | . | X | . | . | . | . | X | . | . | . |
| | | 5486 | No Abnormalities Detected | . | . | X | . | . | . | . | X | . | . |
| | | 5487 | No Abnormalities Detected | . | . | X | . | . | . | . | X | . | . |
| | | 5488 | No Abnormalities Detected | . | . | . | X | . | . | . | . | X | . |
| | | 5489 | No Abnormalities Detected | . | . | . | X | . | . | . | . | X | . |
| | | 5490 | No Abnormalities Detected | . | . | . | . | X | . | . | . | . | X |
| | | 5491 | No Abnormalities Detected | . | . | . | . | X | . | . | . | . | X |
| | | 5492 | No Abnormalities Detected | X | . | . | . | . | X | . | . | . | . |
| | | 5493 | No Abnormalities Detected | X | . | . | . | . | X | . | . | . | . |
| 2 | m | 5514 | No Abnormalities Detected | . | X | . | . | . | . | X | . | . | . |
| | | 5515 | No Abnormalities Detected | . | X | . | . | . | . | X | . | . | . |
| | | 5516 | No Abnormalities Detected | . | . | X | . | . | . | . | X | . | . |
| | | 5517 | No Abnormalities Detected | . | . | X | . | . | . | . | X | . | . |
| | | 5518 | No Abnormalities Detected | . | . | . | X | . | . | . | . | X | . |
| | | 5519 | No Abnormalities Detected | . | . | . | X | . | . | . | . | X | . |
| | | 5520 | No Abnormalities Detected | . | . | . | . | X | . | . | . | . | X |
| | | 5521 | No Abnormalities Detected | . | . | . | . | X | . | . | . | . | X |
| | | 5522 | No Abnormalities Detected | X | . | . | . | . | X | . | . | . | . |
| | | 5523 | No Abnormalities Detected | X | . | . | . | . | X | . | . | . | . |

Severity Codes: X = Present

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

## Attachment F Individual FOB Categorical Observations – Males (cont.)

| | | | | Day numbers relative to Start Date | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Group | Sex | Animal | Clinical Sign | -7 | -6 | -5 | -4 | -3 | 22 | 23 | 24 | 25 | 26 |
| 3 | m | 5544 | No Abnormalities Detected | . | X | . | . | . | . | X | . | . | . |
| | | 5545 | No Abnormalities Detected | . | X | . | . | . | . | X | . | . | . |
| | | 5546 | No Abnormalities Detected | . | . | X | . | . | . | . | X | . | . |
| | | 5547 | No Abnormalities Detected | . | . | X | . | . | . | . | X | . | . |
| | | 5548 | No Abnormalities Detected | . | . | . | X | . | . | . | . | X | . |
| | | 5549 | No Abnormalities Detected | . | . | . | X | . | . | . | . | X | . |
| | | 5550 | No Abnormalities Detected | . | . | . | . | X | . | . | . | . | X |
| | | 5551 | No Abnormalities Detected | . | . | . | . | X | . | . | . | . | X |
| | | 5552 | No Abnormalities Detected | X | . | . | . | . | X | . | . | . | . |
| | | 5553 | No Abnormalities Detected | X | . | . | . | . | X | . | . | . | . |
| 4 | m | 5574 | No Abnormalities Detected | . | X | . | . | . | . | . | . | . | . |
| | | | Soiling, Perineal | . | . | . | . | . | . | U | . | . | . |
| | | 5575 | No Abnormalities Detected | . | X | . | . | . | . | X | . | . | . |
| | | 5576 | No Abnormalities Detected | . | . | X | . | . | . | . | X | . | . |
| | | 5577 | No Abnormalities Detected | . | . | X | . | . | . | . | X | . | . |
| | | 5578 | No Abnormalities Detected | . | . | . | X | . | . | . | . | X | . |
| | | 5579 | No Abnormalities Detected | . | . | . | X | . | . | . | . | X | . |
| | | 5580 | No Abnormalities Detected | . | . | . | . | X | . | . | . | . | X |
| | | 5581 | No Abnormalities Detected | . | . | . | . | X | . | . | . | . | X |
| | | | Soiling, Perineal | . | . | . | . | . | . | . | . | . | U |
| | | 5582 | No Abnormalities Detected | X | . | . | . | . | X | . | . | . | . |
| | | 5583 | No Abnormalities Detected | X | . | . | . | . | X | . | . | . | . |

Severity Codes: X = Present; U = Urine

Group 1 - 0mg/kg Group 2 - 50mg/kg Group 3 - 250mg/kg Group 4 - 500mg/kg

## Attachment G Individual FOB Categorical Observations – Females

| | | | | Day numbers relative to Start Date | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Group | Sex | Animal | Clinical Sign | -7 | -6 | -5 | -4 | -3 | 22 | 23 | 24 | 25 | 26 |
| 1 | f | 5474 | No Abnormalities Detected | . | X | . | . | . | . | X | . | . | . |
| | | 5475 | No Abnormalities Detected | . | X | . | . | . | . | X | . | . | . |
| | | 5476 | No Abnormalities Detected | . | . | X | . | . | . | . | X | . | . |
| | | 5477 | No Abnormalities Detected | . | . | X | . | . | . | . | X | . | . |
| | | 5478 | No Abnormalities Detected | . | . | . | X | . | . | . | . | X | . |
| | | 5479 | No Abnormalities Detected | . | . | . | X | . | . | . | . | X | . |
| | | 5480 | No Abnormalities Detected | . | . | . | . | X | . | . | . | . | X |
| | | 5481 | No Abnormalities Detected | . | . | . | . | X | . | . | . | . | X |
| | | 5482 | No Abnormalities Detected | X | . | . | . | . | X | . | . | . | . |
| | | 5483 | No Abnormalities Detected | X | . | . | . | . | X | . | . | . | . |
| 2 | f | 5504* | No Abnormalities Deected | . | X | . | . | . | . | . | . | . | . |
| | | 5505 | No Abnormalities Detected | . | X | . | . | . | . | X | . | . | . |
| | | 5506 | No Abnormalities Detected | . | . | X | . | . | . | . | X | . | . |
| | | 5507 | No Abnormalities Detected | . | . | X | . | . | . | . | X | . | . |
| | | 5508 | No Abnormalities Detected | . | . | . | X | . | . | . | . | X | . |
| | | 5509 | No Abnormalities Detected | . | . | . | X | . | . | . | . | X | . |
| | | 5510 | No Abnormalities Detected | . | . | . | . | X | . | . | . | . | X |
| | | 5511 | No Abnormalities Detected | . | . | . | . | X | . | . | . | . | X |
| | | 5512 | No Abnormalities Detected | X | . | . | . | . | X | . | . | . | . |
| | | 5513 | No Abnormalities Detected | X | . | . | . | . | X | . | . | . | . |

Severity Codes: X = Present; U = Urine
* Animal excluded from statistical analysis due to being moved from the toxicology group to the reproductive group after baseline testing.

Group 1 - 0mg/kg Group 2 - 50mg/kg Group 3 - 250mg/kg Group 4 - 500mg/kg

## Attachment G Individual FOB Categorical Observations – Females (cont.)

| | | | | Day numbers relative to Start Date | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Group | Sex | Animal | Clinical Sign | -7 | -6 | -5 | -4 | -3 | 22 | 23 | 24 | 25 | 26 |
| 3 | f | 5534 | No Abnormalities Detected | . | X | . | . | . | . | X | . | . | . |
| | | 5535 | No Abnormalities Detected | . | X | . | . | . | . | X | . | . | . |
| | | 5536 | No Abnormalities Detected | . | . | X | . | . | . | . | X | . | . |
| | | 5537 | No Abnormalities Detected | . | . | X | . | . | . | . | X | . | . |
| | | 5538 | No Abnormalities Detected | . | . | . | X | . | . | . | . | X | . |
| | | 5539 | No Abnormalities Detected | . | . | . | X | . | . | . | . | . | . |
| | | | Soiling, Abdominal | . | . | . | . | . | . | . | . | U | . |
| | | | Soiling, Perineal | . | . | . | . | . | . | . | . | U | . |
| | | 5540 | No Abnormalities Detected | . | . | X | . | . | . | . | . | . | X |
| | | 5541 | No Abnormalities Detected | . | . | . | . | X | . | . | . | . | X |
| | | 5542 | No Abnormalities Detected | X | . | . | . | . | X | . | . | . | . |
| | | 5543 | No Abnormalities Detected | X | . | . | . | . | X | . | . | . | . |
| 4 | f | 5564 | No Abnormalities Detected | . | X | . | . | . | . | X | . | . | . |
| | | 5565 | No Abnormalities Detected | . | X | . | . | . | . | X | . | . | . |
| | | 5566 | No Abnormalities Detected | . | . | X | . | . | . | . | X | . | . |
| | | 5567 | No Abnormalities Detected | . | . | X | . | . | . | . | X | . | . |
| | | 5568 | No Abnormalities Detected | . | . | . | X | . | . | . | . | X | . |
| | | 5569 | No Abnormalities Detected | . | . | . | X | . | . | . | . | X | . |
| | | 5570 | No Abnormalities Detected | . | . | . | . | X | . | . | . | . | X |
| | | 5571 | No Abnormalities Detected | . | . | . | . | X | . | . | . | . | X |
| | | 5572 | No Abnormalities Detected | X | . | . | . | . | X | . | . | . | . |
| | | 5573 | No Abnormalities Detected | X | . | . | . | . | X | . | . | . | . |

Severity Codes: X = Present; U = Urine

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

## Attachment H Individual FOB Continuous Data - Males (Baseline)

| Group Sex | Animal ID | Rectal Temperature (°Celsius) | Hindlimb Grip Strength (Grams)[1] | Forelimb Grip Strength (Grams)[1] | Landing Foot Splay (Centimeters)[1] |
|---|---|---|---|---|---|
| 1m | 5484 | 37.3 | 731.7 | 665.0 | 12.3 |
| | 5485 | 37.3 | 878.3 | 745.0 | 14.9 |
| | 5486 | 38.3 | 713.3 | 781.7 | 13.2 |
| | 5487 | 37.7 | 555.0 | 645.0 | 14.8 |
| | 5488 | 37.8 | 946.7 | 768.3 | 12.4 |
| | 5489 | 37.7 | 846.7 | 953.3 | 11.2 |
| | 5490 | 37.4 | 998.3 | 928.3 | 14.9 |
| | 5491 | 37.5 | 998.3 | 1001.7 | 11.5 |
| | 5492 | 37.6 | 688.3 | 681.7 | 14.3 |
| | 5493 | 36.5 | 788.3 | 1015.0 | 14.3 |
| 2m | 5514 | 38.0 | 711.7 | 708.3 | 12.4 |
| | 5515 | 36.6 | 786.7 | 625.0 | 15.0 |
| | 5516 | 38.1 | 743.3 | 1130.0 | 12.4 |
| | 5517 | 37.9 | 710.0 | 681.7 | 12.6 |
| | 5518 | 38.0 | 806.7 | 768.3 | 13.0 |
| | 5519 | 37.5 | 746.7 | 801.7 | 15.2 |
| | 5520 | 37.5 | 881.7 | 913.3 | 11.5 |
| | 5521 | 37.3 | 476.7 | 768.3 | 11.8 |
| | 5522 | 37.8 | 888.3 | 848.3 | 14.4 |
| | 5523 | 36.8 | 756.7 | 848.3 | 13.5 |
| 3m | 5544 | 37.9 | 625.0 | 765.0 | 13.6 |
| | 5545 | 37.7 | 611.7 | 670.0 | 11.8 |
| | 5546 | 38.2 | 680.0 | 735.0 | 10.0 |
| | 5547 | 37.9 | 605.0 | 806.7 | 12.1 |
| | 5548 | 37.9 | 1000.0 | 610.0 | 15.8 |
| | 5549 | 37.7 | 661.7 | 681.7 | 13.9 |
| | 5550 | 37.3 | 685.0 | 670.0 | 14.0 |
| | 5551 | 37.2 | 881.7 | 906.7 | 13.3 |
| | 5552 | 37.6 | 658.3 | 768.3 | 14.9 |
| | 5553 | 37.2 | 640.0 | 838.3 | 14.1 |
| 4m | 5574 | 37.4 | 770.0 | 1115.0 | 12.3 |
| | 5575 | 37.4 | 766.7 | 713.3 | 15.0 |
| | 5576 | 38.5 | 541.7 | 753.3 | 13.6 |
| | 5577 | 37.2 | 740.0 | 753.3 | 10.1 |
| | 5578 | 37.9 | 651.7 | 698.3 | 12.6 |
| | 5579 | 37.4 | 936.7 | 1045.0 | 15.0 |
| | 5580 | 37.6 | 666.7 | 646.7 | 10.8 |
| | 5581 | 37.9 | 791.7 | 688.3 | 10.4 |
| | 5582 | 38.3 | 701.7 | 975.0 | 11.4 |
| | 5583 | 37.6 | 596.7 | 746.7 | 9.2 |

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day
1 Represents the mean of 3 trials

## Attachment I Individual FOB Continuous Data - Males (Treated)

| Group Sex | Animal ID | Rectal Temperature (°Celsius) | Hindlimb Grip Strength (Grams)[1] | Forelimb Grip Strength (Grams)[1] | Landing Foot Splay (Centimeters)[1] |
|---|---|---|---|---|---|
| 1m | 5484 | 38.2 | 1111.7 | 956.7 | 14.8 |
| | 5485 | 37.4 | 1285.0 | 1551.7 | 16.2 |
| | 5486 | 38.4 | 1265.0 | 1306.7 | 13.9 |
| | 5487 | 37.7 | 1270.0 | 791.7 | 14.9 |
| | 5488 | 37.1 | 1390.0 | 976.7 | 10.4 |
| | 5489 | 38.4 | 1060.0 | 1396.7 | 13.5 |
| | 5490 | 38.3 | 1471.7 | 1023.3 | 12.9 |
| | 5491 | 37.5 | 1313.3 | 813.3 | 14.7 |
| | 5492 | 38.4 | 1161.7 | 866.7 | 11.0 |
| | 5493 | 38.1 | 1166.7 | 1086.7 | 9.5 |
| 2m | 5514 | 37.4 | 1395.0 | 1406.7 | 8.7 |
| | 5515 | 38.2 | 1036.7 | 1070.0 | 12.8 |
| | 5516 | 38.6 | 1140.0 | 1180.0 | 11.3 |
| | 5517 | 37.7 | 1108.3 | 1075.0 | 11.2 |
| | 5518 | 38.1 | 1235.0 | 955.0 | 11.3 |
| | 5519 | 37.5 | 1398.3 | 1298.3 | 12.9 |
| | 5520 | 38.0 | 1256.7 | 1115.0 | 12.8 |
| | 5521 | 38.0 | 976.7 | 740.0 | 11.1 |
| | 5522 | 37.9 | 1366.7 | 1021.7 | 13.1 |
| | 5523 | 38.3 | 1306.7 | 1255.0 | 13.8 |
| 3m | 5544 | 38.3 | 1060.0 | 553.3 | 10.0 |
| | 5545 | 38.0 | 1113.3 | 1080.0 | 11.1 |
| | 5546 | 37.7 | 1203.3 | 766.7 | 11.9 |
| | 5547 | 38.0 | 1036.7 | 941.7 | 10.2 |
| | 5548 | 37.7 | 1508.3 | 1001.7 | 11.5 |
| | 5549 | 38.2 | 1101.7 | 836.7 | 13.8 |
| | 5550 | 37.8 | 1250.0 | 1406.7 | 14.1 |
| | 5551 | 37.9 | 1243.3 | 1005.0 | 10.9 |
| | 5552 | 37.9 | 1416.7 | 1340.0 | 13.4 |
| | 5553 | 37.8 | 1421.7 | 1290.0 | 11.2 |
| 4m | 5574 | 37.9 | 1088.3 | 876.7 | 12.1 |
| | 5575 | 37.1 | 843.3 | 1090.0 | 14.1 |
| | 5576 | 38.0 | 1070.0 | 958.3 | 14.9 |
| | 5577 | 37.5 | 948.3 | 828.3 | 11.5 |
| | 5578 | 38.0 | 1081.7 | 838.3 | 11.8 |
| | 5579 | 38.1 | 1488.3 | 1071.7 | 12.6 |
| | 5580 | 37.3 | 1201.7 | 773.3 | 11.5 |
| | 5581 | 37.5 | 1030.0 | 1290.0 | 10.2 |
| | 5582 | 38.4 | 988.3 | 1095.0 | 11.0 |
| | 5583 | 38.0 | 911.7 | 1103.3 | 10.4 |

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day
1Represents the mean of 3 trials

## Attachment J Individual FOB Continuous Data - Females (Baseline)

| Group Sex | Animal ID | RectalTemperature (°Celsius) | Hindlimb Grip Strength (Grams)[1] | Forelimb Grip Strength (Grams)[1] | Landing Foot Splay (Centimeters)[1] |
|---|---|---|---|---|---|
| 1f | 5474 | 38.9 | 693.3 | 601.7 | 11.0 |
| | 5475 | 38.0 | 765.0 | 701.7 | 10.6 |
| | 5476 | 38.3 | 545.0 | 713.3 | 11.7 |
| | 5477 | 38.2 | 508.3 | 660.0 | 10.7 |
| | 5478 | 38.5 | 745.0 | 748.3 | 11.0 |
| | 5479 | 38.2 | 825.0 | 768.3 | 9.3 |
| | 5480 | 38.2 | 863.3 | 760.0 | 10.4 |
| | 5481 | 38.0 | 738.3 | 855.0 | 12.7 |
| | 5482 | 37.9 | 570.0 | 738.3 | 9.2 |
| | 5483 | 36.7 | 678.3 | 671.7 | 10.9 |
| 2f | 5504* | 37.8 | 750.0 | 761.7 | 11.4 |
| | 5505 | 38.1 | 586.7 | 646.7 | 8.5 |
| | 5506 | 37.8 | 605.0 | 773.3 | 7.4 |
| | 5507 | 38.5 | 853.3 | 766.7 | 13.8 |
| | 5508 | 38.0 | 603.3 | 765.0 | 11.0 |
| | 5509 | 38.3 | 603.3 | 766.7 | 8.3 |
| | 5510 | 38.3 | 700.0 | 656.7 | 13.2 |
| | 5511 | 37.7 | 511.7 | 906.7 | 10.8 |
| | 5512 | 37.9 | 745.0 | 756.7 | 11.3 |
| | 5513 | 37.5 | 636.7 | 596.7 | 11.4 |
| 3f | 5534 | 38.2 | 645.0 | 623.3 | 9.6 |
| | 5535 | 38.2 | 593.3 | 676.7 | 10.9 |
| | 5536 | 38.0 | 693.3 | 813.3 | 10.7 |
| | 5537 | 37.3 | 586.7 | 736.7 | 8.2 |
| | 5538 | 38.0 | 608.3 | 781.7 | 8.7 |
| | 5539 | 38.3 | 875.0 | 680.0 | 13.1 |
| | 5540 | 37.5 | 628.3 | 636.7 | 10.3 |
| | 5541 | 38.0 | 848.3 | 898.3 | 13.4 |
| | 5542 | 38.4 | 590.0 | 693.3 | 11.6 |
| | 5543 | 37.5 | 746.7 | 673.3 | 12.4 |
| 4f | 5564 | 38.1 | 530.0 | 623.3 | 10.3 |
| | 5565 | 37.6 | 921.7 | 771.7 | 11.7 |
| | 5566 | 38.3 | 811.7 | 885.0 | 12.7 |
| | 5567 | 38.3 | 861.7 | 733.3 | 12.2 |
| | 5568 | 38.2 | 690.0 | 746.7 | 10.7 |
| | 5569 | 38.1 | 568.3 | 730.0 | 7.7 |
| | 5570 | 38.4 | 833.3 | 850.0 | 7.6 |
| | 5571 | 37.8 | 886.7 | 743.3 | 12.8 |
| | 5572 | 37.4 | 605.0 | 636.7 | 10.7 |
| | 5573 | 37.6 | 481.7 | 716.7 | 12.6 |

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day
[1]Represents the mean of 3 trials
* Animal excluded from statistical analysis due to being moved from the toxicology group to the reproductive group after baseline testing

## Attachment K Individual FOB Continuous Data - Females (Treated)

| Group Sex | Animal ID | RectalTemperature (°Celsius) | Hindlimb Grip Strength (Grams)[1] | Forelimb Grip Strength (Grams)[1] | Landing Foot Splay (Centimeters)[1] |
|---|---|---|---|---|---|
| 1f | 5474 | 38.1 | 965.0 | 711.7 | 9.6 |
| | 5475 | 37.6 | 1015.0 | 880.0 | 9.7 |
| | 5476 | 37.8 | 783.3 | 986.7 | 7.2 |
| | 5477 | 38.1 | 876.7 | 751.7 | 10.9 |
| | 5478 | 38.7 | 880.0 | 973.3 | 11.0 |
| | 5479 | 37.9 | 1258.3 | 696.7 | 9.1 |
| | 5480 | 38.5 | 1018.3 | 960.0 | 8.6 |
| | 5481 | 38.2 | 1100.0 | 1223.3 | 12.7 |
| | 5482 | 38.7 | 1031.7 | 760.0 | 9.4 |
| | 5483 | 38.7 | 1126.7 | 716.7 | 9.5 |
| 2f | 5505 | 38.0 | 1075.0 | 1098.3 | 13.3 |
| | 5506 | 38.7 | 1090.0 | 803.3 | 11.0 |
| | 5507 | 37.9 | 986.7 | 1146.7 | 10.5 |
| | 5508 | 38.2 | 1161.7 | 955.0 | 12.1 |
| | 5509 | 38.7 | 848.3 | 903.3 | 8.6 |
| | 5510 | 38.5 | 1115.0 | 900.0 | 14.7 |
| | 5511 | 38.1 | 905.0 | 1225.0 | 12.6 |
| | 5512 | 38.9 | 935.0 | 908.3 | 8.9 |
| | 5513 | 38.4 | 1056.7 | 843.3 | 10.5 |
| 3f | 5534 | 38.6 | 1033.3 | 710.0 | 10.2 |
| | 5535 | 38.2 | 998.3 | 888.3 | 12.1 |
| | 5536 | 38.6 | 1151.7 | 1038.3 | 9.7 |
| | 5537 | 37.9 | 863.3 | 1585.0 | 8.7 |
| | 5538 | 38.3 | 991.7 | 966.7 | 7.5 |
| | 5539 | 38.4 | 1570.0 | 951.7 | 11.3 |
| | 5540 | 37.8 | 1038.3 | 966.7 | 10.4 |
| | 5541 | 38.8 | 1075.0 | 1080.0 | 11.1 |
| | 5542 | 38.7 | 1101.7 | 973.3 | 10.2 |
| | 5543 | 38.2 | 1260.0 | 765.0 | 9.3 |
| 4f | 5564 | 38.5 | 453.3 | 730.0 | 8.5 |
| | 5565 | 38.1 | 1153.3 | 906.7 | 12.6 |
| | 5566 | 38.3 | 965.0 | 1250.0 | 12.0 |
| | 5567 | 38.7 | 1113.3 | 1253.3 | 11.2 |
| | 5568 | 38.0 | 1203.3 | 923.3 | 6.6 |
| | 5569 | 38.8 | 856.7 | 990.0 | 9.5 |
| | 5570 | 38.4 | 916.7 | 863.3 | 9.4 |
| | 5571 | 38.2 | 1231.7 | 1163.3 | 12.3 |
| | 5572 | 39.0 | 998.3 | 986.7 | 11.8 |
| | 5573 | 38.7 | 965.0 | 835.0 | 10.7 |

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day
[1]Represents the mean of 3 trials

## Attachment L Individual Motor Activity by Interval - Males (Baseline)

| Group Sex | Animal ID | Interval (8 minutes) 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1m | D5484 | 233 | 161 | 132 | 110 | 28 | 0 | 0 | 19 | 95 | 140 | 918 |
| | D5485 | 231 | 141 | 173 | 53 | 26 | 0 | 1 | 0 | 2 | 0 | 627 |
| | D5486 | 218 | 154 | 138 | 97 | 128 | 114 | 46 | 1 | 0 | 0 | 896 |
| | D5487 | 157 | 94 | 15 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 266 |
| | D5488 | 273 | 270 | 121 | 104 | 85 | 0 | 0 | 0 | 0 | 0 | 853 |
| | D5489 | 245 | 151 | 110 | 111 | 69 | 144 | 33 | 2 | 0 | 0 | 865 |
| | D5490 | 206 | 157 | 162 | 196 | 233 | 143 | 90 | 3 | 1 | 0 | 1191 |
| | D5491 | 268 | 260 | 222 | 151 | 133 | 41 | 64 | 6 | 33 | 0 | 1178 |
| | D5492 | 293 | 201 | 208 | 133 | 178 | 145 | 22 | 0 | 0 | 0 | 1180 |
| | D5493 | 259 | 152 | 131 | 132 | 98 | 104 | 98 | 100 | 14 | 0 | 1088 |
| 2m | D5514 | 222 | 241 | 131 | 187 | 204 | 44 | 111 | 0 | 0 | 0 | 1140 |
| | D5515 | 311 | 218 | 181 | 271 | 102 | 25 | 0 | 1 | 0 | 0 | 1109 |
| | D5516 | 187 | 159 | 71 | 59 | 0 | 0 | 0 | 0 | 25 | 5 | 506 |
| | D5517 | 280 | 199 | 93 | 68 | 145 | 21 | 0 | 0 | 0 | 0 | 806 |
| | D5518 | 210 | 172 | 79 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 463 |
| | D5519 | 326 | 309 | 297 | 223 | 222 | 149 | 57 | 0 | 0 | 0 | 1583 |
| | D5520 | 165 | 147 | 118 | 81 | 37 | 27 | 0 | 0 | 3 | 0 | 578 |
| | D5521 | 299 | 298 | 189 | 163 | 8 | 0 | 101 | 30 | 2 | 1 | 1091 |
| | D5522 | 304 | 241 | 176 | 166 | 89 | 57 | 0 | 0 | 0 | 0 | 1033 |
| | D5523 | 290 | 193 | 178 | 103 | 38 | 0 | 0 | 0 | 0 | 0 | 802 |
| 3m | D5544 | 267 | 279 | 134 | 240 | 140 | 58 | 4 | 0 | 0 | 0 | 1122 |
| | D5545 | 196 | 159 | 126 | 53 | 0 | 0 | 0 | 77 | 74 | 1 | 686 |
| | D5546 | 218 | 176 | 165 | 221 | 55 | 122 | 2 | 3 | 0 | 4 | 966 |
| | D5547 | 172 | 144 | 110 | 65 | 1 | 0 | 0 | 0 | 0 | 2 | 494 |
| | D5548 | 186 | 136 | 33 | 44 | 73 | 118 | 20 | 96 | 149 | 48 | 903 |
| | D5549 | 213 | 196 | 210 | 204 | 112 | 136 | 56 | 107 | 67 | 0 | 1301 |
| | D5550 | 204 | 164 | 111 | 92 | 86 | 96 | 55 | 95 | 51 | 0 | 954 |
| | D5551 | 258 | 232 | 145 | 117 | 107 | 16 | 0 | 0 | 0 | 0 | 875 |
| | D5552 | 171 | 130 | 49 | 48 | 5 | 0 | 0 | 0 | 0 | 0 | 403 |
| | D5553 | 235 | 176 | 231 | 39 | 0 | 0 | 0 | 8 | 0 | 3 | 692 |
| 4m | D5574 | 222 | 202 | 141 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 565 |
| | D5575 | 243 | 89 | 8 | 0 | 0 | 0 | 0 | 0 | 0 | 16 | 356 |
| | D5576 | 169 | 122 | 94 | 99 | 12 | 103 | 102 | 1 | 0 | 0 | 702 |
| | D5577 | 173 | 92 | 31 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 298 |
| | D5578 | 294 | 204 | 179 | 177 | 163 | 93 | 80 | 0 | 3 | 0 | 1193 |
| | D5579 | 218 | 169 | 267 | 226 | 52 | 9 | 3 | 0 | 0 | 0 | 944 |
| | D5580 | 155 | 137 | 56 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 348 |
| | D5581 | 297 | 234 | 89 | 110 | 79 | 28 | 0 | 0 | 1 | 0 | 838 |
| | D5582 | 216 | 131 | 115 | 69 | 26 | 0 | 1 | 1 | 0 | 3 | 562 |
| | D5583 | 219 | 175 | 170 | 119 | 15 | 0 | 0 | 1 | 0 | 2 | 701 |

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day

## Attachment M Individual Motor Activity by Interval - Males (Treated)

| Group Sex | Animal ID | Intervals (8 minutes each) 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1m | D5484 | 165 | 152 | 85 | 82 | 66 | 84 | 94 | 70 | 51 | 42 | 891 |
| | D5485 | 156 | 113 | 53 | 16 | 57 | 88 | 8 | 26 | 65 | 32 | 614 |
| | D5486 | 214 | 228 | 93 | 67 | 67 | 59 | 112 | 41 | 13 | 112 | 1006 |
| | D5487 | 188 | 100 | 64 | 69 | 0 | 0 | 0 | 0 | 0 | 3 | 424 |
| | D5488 | 300 | 284 | 73 | 0 | 0 | 0 | 107 | 73 | 0 | 6 | 843 |
| | D5489 | 284 | 164 | 82 | 53 | 57 | 84 | 15 | 7 | 0 | 24 | 770 |
| | D5490 | 236 | 134 | 144 | 9 | 47 | 9 | 4 | 0 | 8 | 17 | 608 |
| | D5491 | 236 | 197 | 111 | 97 | 66 | 94 | 102 | 83 | 113 | 64 | 1163 |
| | D5492 | 234 | 148 | 92 | 42 | 35 | 5 | 3 | 0 | 0 | 1 | 560 |
| | D5493 | 234 | 211 | 111 | 63 | 0 | 69 | 69 | 6 | 5 | 13 | 781 |
| 2m | D5514 | 165 | 147 | 163 | 3 | 0 | 0 | 0 | 34 | 54 | 0 | 566 |
| | D5515 | 311 | 260 | 229 | 27 | 94 | 57 | 48 | 2 | 48 | 20 | 1096 |
| | D5516 | 167 | 115 | 63 | 47 | 0 | 0 | 79 | 54 | 0 | 0 | 525 |
| | D5517 | 260 | 98 | 172 | 36 | 87 | 105 | 64 | 33 | 71 | 85 | 1011 |
| | D5518 | 212 | 128 | 71 | 50 | 95 | 29 | 25 | 78 | 69 | 54 | 811 |
| | D5519 | 340 | 202 | 124 | 120 | 243 | 151 | 53 | 7 | 20 | 0 | 1260 |
| | D5520 | 146 | 117 | 73 | 2 | 0 | 27 | 17 | 1 | 2 | 2 | 387 |
| | D5521 | 376 | 290 | 200 | 153 | 50 | 99 | 83 | 0 | 64 | 56 | 1371 |
| | D5522 | 188 | 159 | 86 | 32 | 6 | 7 | 65 | 98 | 118 | 12 | 771 |
| | D5523 | 316 | 202 | 161 | 74 | 76 | 34 | 5 | 61 | 6 | 0 | 935 |
| 3m | D5544 | 220 | 256 | 169 | 98 | 1 | 0 | 0 | 10 | 118 | 84 | 956 |
| | D5545 | 167 | 115 | 84 | 100 | 81 | 75 | 11 | 0 | 0 | 0 | 633 |
| | D5546 | 190 | 119 | 117 | 69 | 89 | 39 | 51 | 27 | 0 | 47 | 748 |
| | D5547 | 157 | 104 | 103 | 87 | 87 | 56 | 54 | 0 | 0 | 0 | 648 |
| | D5548 | 182 | 112 | 115 | 84 | 23 | 58 | 95 | 87 | 15 | 0 | 771 |
| | D5549 | 247 | 168 | 133 | 110 | 77 | 72 | 89 | 64 | 29 | 31 | 1020 |
| | D5550 | 186 | 136 | 112 | 77 | 65 | 28 | 69 | 8 | 0 | 82 | 763 |
| | D5551 | 196 | 124 | 73 | 27 | 94 | 114 | 56 | 1 | 0 | 0 | 685 |
| | D5552 | 106 | 62 | 49 | 0 | 1 | 1 | 0 | 21 | 0 | 0 | 240 |
| | D5553 | 259 | 204 | 69 | 8 | 0 | 7 | 0 | 84 | 57 | 11 | 699 |
| 4m | D5574 | 213 | 121 | 126 | 63 | 114 | 126 | 77 | 69 | 23 | 0 | 932 |
| | D5575 | 282 | 164 | 99 | 44 | 7 | 28 | 39 | 3 | 5 | 0 | 671 |
| | D5576 | 234 | 126 | 136 | 16 | 0 | 0 | 17 | 0 | 1 | 1 | 531 |
| | D5577 | 250 | 134 | 59 | 64 | 32 | 25 | 4 | 2 | 1 | 10 | 581 |
| | D5578 | 225 | 128 | 19 | 41 | 62 | 4 | 0 | 7 | 1 | 70 | 557 |
| | D5579 | 181 | 158 | 88 | 78 | 60 | 68 | 8 | 0 | 0 | 0 | 641 |
| | D5580 | 212 | 132 | 116 | 90 | 74 | 157 | 48 | 2 | 17 | 82 | 930 |
| | D5581 | 239 | 133 | 151 | 89 | 65 | 13 | 0 | 1 | 8 | 24 | 723 |
| | D5582 | 194 | 93 | 81 | 21 | 66 | 31 | 0 | 5 | 0 | 0 | 491 |
| | D5583 | 262 | 220 | 124 | 28 | 0 | 0 | 0 | 1 | 0 | 38 | 673 |

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day

## Attachment N Individual Motor Activity by Interval - Females (Baseline)

| Group Sex | Animal ID | Intervals (8 minutes each) 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1f | D5474 | 241 | 159 | 105 | 36 | 0 | 0 | 0 | 69 | 97 | 85 | 792 |
| | D5475 | 311 | 190 | 176 | 137 | 211 | 81 | 271 | 88 | 0 | 0 | 1465 |
| | D5476 | 217 | 135 | 65 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 420 |
| | D5477 | 222 | 217 | 220 | 131 | 118 | 129 | 133 | 133 | 203 | 118 | 1624 |
| | D5478 | 289 | 269 | 251 | 201 | 229 | 216 | 178 | 156 | 176 | 146 | 2111 |
| | D5479 | 254 | 243 | 134 | 161 | 119 | 131 | 160 | 88 | 5 | 0 | 1295 |
| | D5480 | 333 | 167 | 197 | 147 | 135 | 144 | 86 | 163 | 99 | 66 | 1537 |
| | D5481 | 200 | 169 | 113 | 143 | 121 | 123 | 152 | 96 | 0 | 0 | 1117 |
| | D5482 | 247 | 171 | 181 | 150 | 129 | 86 | 71 | 47 | 0 | 0 | 1082 |
| | D5483 | 204 | 191 | 122 | 86 | 84 | 89 | 105 | 69 | 83 | 96 | 1129 |
| | D5504* | 276 | 223 | 103 | 68 | 35 | 0 | 1 | 0 | 0 | 0 | 706 |
| 2f | D5505 | 317 | 170 | 101 | 102 | 82 | 0 | 0 | 0 | 0 | 0 | 772 |
| | D5506 | 183 | 174 | 105 | 36 | 0 | 51 | 97 | 0 | 0 | 0 | 646 |
| | D5507 | 280 | 204 | 135 | 141 | 86 | 74 | 92 | 5 | 0 | 6 | 1023 |
| | D5508 | 265 | 121 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 386 |
| | D5509 | 302 | 222 | 228 | 145 | 137 | 96 | 62 | 0 | 0 | 0 | 1192 |
| | D5510 | 223 | 158 | 94 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 477 |
| | D5511 | 209 | 140 | 6 | 80 | 0 | 0 | 5 | 63 | 85 | 0 | 588 |
| | D5512 | 270 | 177 | 155 | 79 | 87 | 87 | 64 | 4 | 64 | 16 | 1003 |
| | D5513 | 235 | 179 | 118 | 94 | 82 | 88 | 7 | 0 | 0 | 0 | 803 |
| 3f | D5534 | 274 | 161 | 124 | 72 | 0 | 0 | 0 | 65 | 102 | 109 | 907 |
| | D5535 | 254 | 118 | 79 | 78 | 129 | 0 | 26 | 0 | 0 | 2 | 686 |
| | D5536 | 322 | 253 | 143 | 110 | 169 | 89 | 128 | 83 | 0 | 0 | 1297 |
| | D5537 | 323 | 223 | 152 | 99 | 0 | 0 | 0 | 0 | 117 | 61 | 975 |
| | D5538 | 268 | 202 | 193 | 94 | 0 | 0 | 0 | 0 | 0 | 0 | 757 |
| | D5539 | 205 | 134 | 91 | 108 | 124 | 2 | 0 | 0 | 0 | 0 | 664 |
| | D5540 | 245 | 173 | 103 | 160 | 40 | 1 | 3 | 0 | 0 | 0 | 725 |
| | D5541 | 302 | 250 | 155 | 135 | 149 | 224 | 185 | 37 | 265 | 297 | 1999 |
| | D5542 | 269 | 168 | 141 | 148 | 104 | 10 | 0 | 42 | 145 | 98 | 1125 |
| | D5543 | 218 | 211 | 133 | 99 | 80 | 48 | 85 | 98 | 22 | 1 | 995 |
| 4f | D5564 | 237 | 196 | 133 | 50 | 68 | 147 | 32 | 0 | 0 | 0 | 863 |
| | D5565 | 256 | 164 | 95 | 30 | 48 | 0 | 0 | 0 | 0 | 3 | 596 |
| | D5566 | 231 | 213 | 59 | 11 | 41 | 28 | 0 | 0 | 0 | 0 | 583 |
| | D5567 | 255 | 197 | 191 | 52 | 0 | 0 | 1 | 0 | 0 | 0 | 696 |
| | D5568 | 243 | 151 | 96 | 30 | 0 | 0 | 5 | 0 | 0 | 0 | 525 |
| | D5569 | 264 | 203 | 201 | 137 | 99 | 1 | 85 | 105 | 53 | 2 | 1150 |
| | D5570 | 198 | 163 | 171 | 119 | 125 | 112 | 116 | 72 | 65 | 2 | 1143 |
| | D5571 | 198 | 166 | 107 | 146 | 16 | 0 | 0 | 0 | 0 | 0 | 633 |
| | D5572 | 200 | 190 | 155 | 128 | 125 | 107 | 110 | 110 | 73 | 68 | 1266 |
| | D5573 | 237 | 162 | 160 | 139 | 141 | 79 | 28 | 0 | 0 | 0 | 946 |

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day

* Animal excluded from statistical analysis due to being moved from the toxicology group to the reproductive group after baseline testing.

## Attachment O Individual Motor Activity by Interval - Females (Treated)

Intervals (8 minutes each)

| Group Sex | Animal ID | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1f | D5474 | 245 | 132 | 116 | 103 | 159 | 162 | 175 | 162 | 132 | 93 | 1479 |
| | D5475 | 268 | 193 | 167 | 196 | 259 | 404 | 133 | 205 | 154 | 193 | 2172 |
| | D5476 | 211 | 127 | 63 | 1 | 0 | 0 | 0 | 0 | 71 | 154 | 627 |
| | D5477 | 310 | 302 | 290 | 191 | 216 | 110 | 192 | 105 | 46 | 0 | 1762 |
| | D5478 | 267 | 260 | 197 | 185 | 165 | 117 | 104 | 42 | 53 | 103 | 1493 |
| | D5479 | 213 | 171 | 179 | 139 | 111 | 125 | 89 | 140 | 113 | 136 | 1416 |
| | D5480 | 263 | 252 | 119 | 3 | 40 | 1 | 0 | 77 | 84 | 74 | 913 |
| | D5481 | 224 | 150 | 123 | 93 | 118 | 43 | 105 | 146 | 24 | 0 | 1026 |
| | D5482 | 207 | 126 | 96 | 77 | 79 | 97 | 86 | 57 | 26 | 92 | 943 |
| | D5483 | 247 | 199 | 154 | 170 | 110 | 142 | 87 | 152 | 126 | 82 | 1469 |
| 2f | D5505 | 229 | 174 | 177 | 150 | 125 | 67 | 154 | 94 | 109 | 123 | 1402 |
| | D5506 | 139 | 125 | 107 | 53 | 2 | 2 | 0 | 0 | 31 | 66 | 525 |
| | D5507 | 145 | 106 | 107 | 91 | 85 | 117 | 114 | 100 | 33 | 49 | 947 |
| | D5508 | 208 | 166 | 111 | 20 | 82 | 66 | 13 | 0 | 0 | 0 | 666 |
| | D5509 | 247 | 250 | 160 | 200 | 148 | 87 | 30 | 107 | 32 | 0 | 1261 |
| | D5510 | 161 | 136 | 54 | 0 | 0 | 0 | 0 | 2 | 5 | 126 | 484 |
| | D5511 | 204 | 166 | 101 | 130 | 124 | 125 | 102 | 54 | 85 | 100 | 1191 |
| | D5512 | 249 | 212 | 184 | 183 | 128 | 41 | 40 | 2 | 97 | 87 | 1223 |
| | D5513 | 241 | 161 | 96 | 78 | 107 | 74 | 2 | 118 | 80 | 81 | 1038 |
| 3f | D5534 | 236 | 218 | 171 | 84 | 116 | 74 | 115 | 92 | 90 | 91 | 1287 |
| | D5535 | 170 | 151 | 158 | 56 | 111 | 70 | 157 | 34 | 77 | 90 | 1074 |
| | D5536 | 204 | 158 | 96 | 30 | 5 | 0 | 143 | 88 | 76 | 35 | 835 |
| | D5537 | 247 | 209 | 211 | 190 | 148 | 63 | 83 | 3 | 7 | 4 | 1165 |
| | D5538 | 215 | 150 | 117 | 121 | 87 | 64 | 49 | 34 | 136 | 105 | 1078 |
| | D5539 | 161 | 136 | 136 | 60 | 34 | 59 | 60 | 32 | 0 | 1 | 679 |
| | D5540 | 211 | 112 | 92 | 90 | 82 | 49 | 60 | 0 | 0 | 91 | 787 |
| | D5541 | 288 | 226 | 219 | 163 | 222 | 203 | 133 | 72 | 148 | 24 | 1698 |
| | D5542 | 172 | 144 | 144 | 85 | 118 | 65 | 30 | 76 | 86 | 44 | 964 |
| | D5543 | 202 | 113 | 114 | 85 | 53 | 76 | 49 | 79 | 4 | 1 | 776 |
| 4f | D5564 | 238 | 114 | 133 | 54 | 58 | 31 | 132 | 129 | 73 | 77 | 1039 |
| | D5565 | 246 | 163 | 131 | 70 | 53 | 105 | 59 | 54 | 86 | 52 | 1019 |
| | D5566 | 273 | 183 | 146 | 56 | 0 | 0 | 114 | 42 | 110 | 35 | 959 |
| | D5567 | 214 | 203 | 178 | 175 | 70 | 71 | 0 | 69 | 150 | 48 | 1178 |
| | D5568 | 175 | 107 | 75 | 82 | 65 | 76 | 80 | 58 | 42 | 71 | 831 |
| | D5569 | 214 | 176 | 175 | 158 | 119 | 98 | 100 | 101 | 117 | 50 | 1308 |
| | D5570 | 170 | 142 | 145 | 129 | 123 | 53 | 57 | 20 | 86 | 49 | 974 |
| | D5571 | 223 | 135 | 142 | 82 | 40 | 65 | 80 | 42 | 45 | 33 | 887 |
| | D5572 | 205 | 164 | 67 | 66 | 109 | 79 | 26 | 0 | 1 | 41 | 758 |
| | D5573 | 174 | 153 | 81 | 104 | 111 | 118 | 121 | 75 | 27 | 46 | 1010 |

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 50 mg/kg/day Group 3 – 250 mg/kg/day Group 4 – 500 mg/kg/day

# APPENDIX N

## Clinical Pathology

## Results, Summaries, and Individual Animal Data

# Appendix N

## Clinical Pathology

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# Appendix N

## Clinical Pathology

## 1. METHODS

Female and male rats were exposed to dimethysilanediol (DMSD) at concentrations of 0, 50, 250, and 500 mg/kg/day. Only the toxicology groups were scheduled for clinical pathology analysis. There were 10 female and 10 male rats in groups 1, 3, and 4 of the toxicology exposure groups. Only 9 females were analyzed for group 1 due to inadequate volume due to clotting at collection for Animal D5474. Group 2 had 9 females due to removal of animal D5504 for replacement in the reproductive group. In group 3, animal D5538 did not have sufficient volume to analyze for hematology or coagulation.

Analysis of the clinical chemistry was conducted with the Cobas Integra 400 Plus®, Serial Number 39-5089 (Roche Diagnostics Corporation, Indianapolis, IN). The samples were analyzed for the following parameters:

| | | |
|---|---|---|
| Alkaline phosphatase | Alanine aminotransferase | Aspartate aminotransferase |
| Total bilirubin | Albumin | Total Protein |
| BUN | Creatinine | Glucose |
| Cholesterol | Calcium | Phosphorus (phosphate) |
| Sodium | Potassium | Chloride |

Specific methodologies for the parameters measured are in Attachment 1 of this document. All samples were analyzed on the day of blood collection. Individual data are presented in Attachment 2.

Hematology analysis was conducted with the Cell Dyn 3700 Hematology Analyzer, Serial Number 1991AN96, (Abbott Diagnostics, Dallas, TX). The samples were analyzed for the following parameters:

| | | |
|---|---|---|
| White blood cell | Red blood cell | Hemoglobin |
| Hematocrit | MCV | MCH |
| MCHC | Platelets | Neutrophils |
| Lymphocytes | Monocytes | Eosinophils |
| Basophils | | |

Specific methodologies for the parameters measured are in Attachment 1 of this document. Blood specimens for females collected on Day 29 were stored refrigerated (2-8°C) and analyzed on Day 30. Blood specimens for males were collected and analyzed on Day 30. Individual data are presented in Attachment 2.

Prothrombin times were analyzed using rabbit brain calcium thromboplastin with the ACL 100 Coagulation Analyzer, Serial Number 030710733, (Instrumentation Laboratories, Lexington, MA ) using nephalometry methodology. All samples were analyzed on the day of blood collection. Individual data are presented in Attachment 2.

## Appendix N

## Clinical Pathology

## 2. DATA ANALYSIS

Clinical pathology data was collected in Provantis™ version 6.5 and statistically evaluated with Provantis™ version 8.2 and SAS 9.13. Statistically significant probabilities were reported for $p$ values of < 0.05 and < 0.01.

Clinical chemistry, hematology data, and prothrombin times were analyzed using a One-way Analysis of Variance (ANOVA). Data was tested for homogeneity of variances (Bartlett's) and normality of distributions (Wilks-Shapiro). If requirements for these tests were not met, a log or rank transformation was performed. If the ANOVA was significant, pair-wise comparisons of the exposed groups to control were made using the Dunnett's Test.

## 3. RESULTS

Clinical Chemistry

Statistical significant differences were seen in the female toxicology rats (Table 1) for alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total bilirubin, and cholesterol. These parameters were initially analyzed using the one-way ANOVA, then a pairwise comparison by Dunnett's Test.

A significant difference for alanine aminotransferase and cholesterol ($p$<0.01) was seen in group 4. The aspartate aminotransferase was statistically significant ($p$<0.05) for group 2. The alkaline phosphatase ($p$<0.01) and total bilirubin ( $p$<0.05) were statistically different in groups 3 and 4 of both parameters. Although these parameters were statistically significant, they were within historical control ranges of this laboratory (Attachment 3).

In male rats (Table 2), the alkaline phosphatase and total bilirubin were statistically different in groups 3 and 4 ($p$<0.01). Alanine aminotransferase, BUN, and sodium had significant differences for group 4 ($p$<0.01). Significant differences ($p$ <0.05) were seen for albumin in group 3 and total protein in group 4. These parameters were within the historical ranges (Attachment 3). The aspartate aminotransferase had statistical differences for groups 2 ($p$<0.05), 3 and 4 ($p$<0.01). The mean values for group 4 (48.8 U/L) was below the historical range (55-129 U/L).

There were no significant differences noted in the other clinical chemistry parameters across groups for either sex.

Hematology

Statistically significant decreases were seen in group 4 in the female toxicology rats (Table 3) for hemoglobin and mean cell hemoglobin concentration ($p$ <0.01). These were both within the historical ranges.

The male rats (Table 4) in group 4 had significant decreases for hemoglobin and mean cell hemoglobin ($p$ <0.01) and hematocrit ($p$ <0.05). The group mean values for hemoglobin (13.49

g/dL) and hematocrit (39.63 %) were slightly below the individual animal historical range (13.6-16.1 g/dL and 40.0-45.9%, respectively). The mean cell hemoglobin was within the historical range.

There were no significant differences noted in the other hematology parameters across groups for either sex.

Prothrombin Times

Statistically significant decreases ($p<0.01$) were seen in groups 3 and 4 for female toxicology rats (Table 5) for prothrombin times . Statistically significant increases ($p<0.01$) were seen in groups 3 and 4 for male rats (Table 6). The individual animal values in this study were within the range of historical controls.

## 4. REFERENCES

1. Cobas Integra 400 Methods Manual, Roche Diagnostics, Indianapolis, IN, 2004

2. Cell Dyn 3700 Operator Manual, Abbott Park, IL, 2003

3. Provantis™ Statistics User Guide, Document Version 2.3, Instem LSS, Stone, England, 2007

# Appendix N

## Clinical Pathology

### TABLE 1: Summary of Clinical Chemistry –Female Rats

Day: 29 Relative to Start Date

| | | Group 1 0mg/kg | Group 2 50mg/kg | Group 3 250mg/kg | Group 4 500mg/kg |
|---|---|---|---|---|---|
| ALP ** 1 (U/L) | Mean | 82.9 | 75.1 | 58.8 ** 2 | 48.3 ** 2 |
| | SD | 17.8 | 17.8 | 17.2 | 14.1 |
| | N | 9 | 9 | 10 | 10 |
| ALT ** 1 (U/L) | Mean | 19.2 | 19.7 | 22.0 | 26.9 ** 2 |
| | SD | 4.2 | 3.9 | 4.8 | 4.9 |
| | N | 9 | 9 | 10 | 10 |
| AST * 3 (U/L) | Mean | 60.7 | 76.0 * 4 | 68.1 | 59.3 |
| | SD | 7.7 | 9.6 | 12.8 | 15.1 |
| | N | 9 | 9 | 10 | 10 |
| TBILI ** 1 (mg/dL) | Mean | 0.124 | 0.132 | 0.092 * 4 | 0.088 * 4 |
| | SD | 0.025 | 0.019 | 0.023 | 0.033 |
| | N | 9 | 9 | 10 | 10 |
| ALB (g/dL) | Mean | 4.06 | 4.16 | 4.06 | 3.86 |
| | SD | 0.18 | 0.22 | 0.34 | 0.23 |
| | N | 9 | 9 | 10 | 10 |
| TP * 3 (g/dL) | Mean | 6.02 | 5.88 | 6.03 | 6.37 |
| | SD | 0.26 | 0.41 | 0.33 | 0.25 |
| | N | 9 | 9 | 10 | 10 |
| BUN (mg/dL) | Mean | 13.2 | 13.3 | 14.2 | 15.7 |
| | SD | 2.8 | 2.3 | 2.5 | 2.1 |
| | N | 9 | 9 | 10 | 10 |
| CREAT (mg/dL) | Mean | 0.33 | 0.32 | 0.33 | 0.33 |
| | SD | 0.05 | 0.07 | 0.05 | 0.07 |
| | N | 9 | 9 | 10 | 10 |
| GLUC (mg/dL) | Mean | 135.7 | 127.4 | 124.4 | 124.8 |
| | SD | 12.7 | 14.2 | 15.7 | 9.6 |
| | N | 9 | 9 | 10 | 10 |
| CHOL ** 1 (mg/dL) | Mean | 56.3 | 57.1 | 62.5 | 85.7 ** 2 |
| | SD | 6.8 | 13.6 | 12.0 | 10.6 |
| | N | 9 | 9 | 10 | 10 |

** 1 - 1% significance level - Group Factor 1 Way ANOVA
** 2 - 1% significance level - Dunnett's pairwise comparison
* 3 - 5% significance level - Group Factor 1 Way ANOVA
* 4 - 5% significance level - Dunnett's pairwise comparison

# Appendix N

## Clinical Pathology

### TABLE 1 (continued): Summary of Clinical Chemistry -Female Rats

Day: 29 Relative to Start Date

| Sex: Female | | Group 1 0mg/kg | Group 2 50mg/kg | Group 3 250mg/kg | Group 4 500mg/kg |
|---|---|---|---|---|---|
| CA (mg/dL) | Mean | 9.86 | 9.82 | 9.79 | 9.92 |
| | SD | 0.29 | 0.35 | 0.34 | 0.29 |
| | N | 9 | 9 | 10 | 10 |
| PHOS (mg/dL) | Mean | 7.01 | 7.03 | 6.61 | 6.37 |
| | SD | 0.72 | 0.58 | 0.50 | 0.59 |
| | N | 9 | 9 | 10 | 10 |
| NA (mmol/L) | Mean | 139.8 | 140.1 | 139.6 | 138.5 |
| | SD | 0.7 | 1.5 | 1.6 | 1.2 |
| | N | 9 | 9 | 10 | 10 |
| K (mmol/L) | Mean | 4.11 | 4.11 | 4.07 | 3.99 |
| | SD | 0.16 | 0.25 | 0.16 | 0.19 |
| | N | 9 | 9 | 10 | 10 |
| CL (mmol/L) | Mean | 104.1 | 103.8 | 103.5 | 102.8 |
| | SD | 1.5 | 1.4 | 1.0 | 1.4 |
| | N | 9 | 9 | 10 | 10 |

# Appendix N

## Clinical Pathology

### TABLE 2: Summary of Clinical Chemistry –Male Rats

Day: 30 Relative to Start Date

| Sex: Male | | Group 1 0mg/kg | Group 2 50mg/kg | Group 3 250mg/kg | Group 4 500mg/kg |
|---|---|---|---|---|---|
| ALP ** 1 (U/L) | Mean | 140.7 | 133.3 | 100.0 ** 2 | 89.8 ** 2 |
| | SD | 43.2 | 27.1 | 21.6 | 20.9 |
| | N | 10 | 10 | 10 | 10 |
| ALT ** 1 (U/L) | Mean | 17.6 | 21.5 | 20.5 | 27.1 ** 2 |
| | SD | 3.4 | 3.7 | 3.5 | 8.4 |
| | N | 10 | 10 | 10 | 10 |
| AST ** 1 (U/L) | Mean | 85.5 | 70.8 * 3 | 58.0 ** 2 | 48.8 ** 2 |
| | SD | 13.8 | 13.1 | 8.7 | 5.1 |
| | N | 10 | 10 | 10 | 10 |
| TBILI ** 1 (mg/dL) | Mean | 0.122 | 0.103 | 0.086 ** 2 | 0.084 ** 2 |
| | SD | 0.031 | 0.013 | 0.017 | 0.024 |
| | N | 10 | 10 | 10 | 10 |
| ALB * 4 (g/dL) | Mean | 3.72 | 3.69 | 3.57 * 3 | 3.62 |
| | SD | 0.16 | 0.11 | 0.07 | 0.11 |
| | N | 10 | 10 | 10 | 10 |
| TP * 4 (g/dL) | Mean | 5.69 | 5.78 | 5.70 | 5.94 * 3 |
| | SD | 0.22 | 0.19 | 0.25 | 0.14 |
| | N | 10 | 10 | 10 | 10 |
| BUN ** 1 (mg/dL) | Mean | 11.3 | 12.2 | 13.1 | 14.4 ** 2 |
| | SD | 1.3 | 1.9 | 2.0 | 2.1 |
| | N | 10 | 10 | 10 | 10 |
| CREAT (mg/dL) | Mean | 0.31 | 0.29 | 0.29 | 0.28 |
| | SD | 0.03 | 0.03 | 0.03 | 0.04 |
| | N | 10 | 10 | 10 | 10 |
| GLUC (mg/dL) | Mean | 136.6 | 138.8 | 141.8 | 143.5 |
| | SD | 8.8 | 15.8 | 19.9 | 9.3 |
| | N | 10 | 10 | 10 | 10 |
| CHOL (mg/dL) | Mean | 47.8 | 44.6 | 45.7 | 48.6 |
| | SD | 11.8 | 10.5 | 9.1 | 12.3 |
| | N | 10 | 10 | 10 | 10 |

** 1 - 1% significance level - Group Factor 1 Way ANOVA
** 2 - 1% significance level - Dunnett's pairwise comparison
* 3 - 5% significance level - Dunnett's pairwise comparison
* 4 - 5% significance level - Group Factor 1 Way ANOVA

# Appendix N

## Clinical Pathology

### TABLE 2(continued): Summary of Clinical Chemistry –Male Rats

Day: 30 Relative to Start Date

| Sex: Male | | Group 1 0mg/kg | Group 2 50mg/kg | Group 3 250mg/kg | Group 4 500mg/kg |
|---|---|---|---|---|---|
| CA (mg/dL) | Mean | 9.78 | 9.85 | 9.85 | 10.00 |
| | SD | 0.34 | 0.28 | 0.23 | 0.27 |
| | N | 10 | 10 | 10 | 10 |
| PHOS (mg/dL) | Mean | 7.58 | 7.69 | 7.60 | 7.20 |
| | SD | 0.62 | 0.56 | 0.79 | 0.51 |
| | N | 10 | 10 | 10 | 10 |
| NA ** 1 (mmol/L) | Mean | 141.4 | 140.8 | 140.8 | 139.8 ** 2 |
| | SD | 0.8 | 1.1 | 0.6 | 0.9 |
| | N | 10 | 10 | 10 | 10 |
| K (mmol/L) | Mean | 4.50 | 4.43 | 4.49 | 4.43 |
| | SD | 0.22 | 0.22 | 0.25 | 0.25 |
| | N | 10 | 10 | 10 | 10 |
| CL (mmol/L) | Mean | 102.8 | 102.0 | 103.0 | 102.9 |
| | SD | 1.3 | 0.8 | 1.1 | 1.4 |
| | N | 10 | 10 | 10 | 10 |

** 1 - 1% significance level - Group Factor 1 Way ANOVA
** 2 - 1% significance level - Dunnett's pairwise comparison

# Appendix N

## Clinical Pathology

### TABLE 3: Summary of Hematology Data –Female Rats

Day: 29 Relative to Start Date

| Sex: Female | | Group 1 0mg/kg | Group 2 50mg/kg | Group 3 250mg/kg | Group 4 500mg/kg |
|---|---|---|---|---|---|
| WBC ($10^3$/uL) | Mean | 5.06 | 5.48 | 5.47 | 5.57 |
| | SD | 1.85 | 1.62 | 1.62 | 1.41 |
| | N | 9 | 9 | 9 | 10 |
| RBC ($10^6$/uL) | Mean | 7.399 | 7.394 | 7.434 | 7.327 |
| | SD | 0.323 | 0.382 | 0.292 | 0.139 |
| | N | 9 | 9 | 9 | 10 |
| HGB ** 1 (g/dL) | Mean | 14.52 | 14.50 | 14.16 | 13.92 ** 2 |
| | SD | 0.40 | 0.42 | 0.47 | 0.32 |
| | N | 9 | 9 | 9 | 10 |
| HCT (%) | Mean | 43.01 | 43.12 | 42.22 | 42.02 |
| | SD | 1.14 | 1.24 | 1.74 | 1.07 |
| | N | 9 | 9 | 9 | 10 |
| MCV (fL) | Mean | 58.22 | 58.41 | 56.82 | 57.34 |
| | SD | 2.40 | 2.35 | 1.75 | 1.59 |
| | N | 9 | 9 | 9 | 10 |
| MCH * 3 (pg) | Mean | 19.66 | 19.67 | 19.06 | 19.00 |
| | SD | 0.76 | 0.72 | 0.58 | 0.44 |
| | N | 9 | 9 | 9 | 10 |
| MCHC ** 1 (g/dL) | Mean | 33.78 | 33.68 | 33.52 | 33.13 ** 2 |
| | SD | 0.36 | 0.30 | 0.37 | 0.36 |
| | N | 9 | 9 | 9 | 10 |
| PLT ($10^3$/uL) | Mean | 1183.78 | 1185.11 | 1182.00 | 1113.00 |
| | SD | 106.41 | 109.47 | 173.29 | 121.03 |
| | N | 9 | 9 | 9 | 10 |

** 1 - 1% significance level - Group Factor 1 Way ANOVA
** 2 - 1% significance level - Dunnett's pairwise comparison
* 3 - 5% significance level - Group Factor 1 Way ANOVA

# Appendix N

## Clinical Pathology

### TABLE 3 (continued): Summary of Hematology Data –Female Rats

Day: 29 Relative to Start Date

| Sex: Female | | Group 1 0mg/kg | Group 2 50mg/kg | Group 3 250mg/kg | Group 4 500mg/kg |
|---|---|---|---|---|---|
| Neutro (%) | Mean | 18.42 | 12.07 | 13.92 | 16.26 |
| | SD | 7.08 | 5.95 | 6.90 | 8.67 |
| | N | 9 | 9 | 9 | 10 |
| Abs Neut ($10^3$/uL) | Mean | 0.8704 | 0.6211 | 0.8207 | 0.9216 |
| | SD | 0.3336 | 0.2836 | 0.6115 | 0.6555 |
| | N | 9 | 9 | 9 | 10 |
| Lymph (%) | Mean | 70.68 | 78.77 | 75.94 | 72.98 |
| | SD | 8.18 | 6.13 | 7.56 | 9.41 |
| | N | 9 | 9 | 9 | 10 |
| Abs Lymph ($10^3$/uL) | Mean | 3.6156 | 4.3722 | 4.0878 | 4.0270 |
| | SD | 1.5931 | 1.5565 | 1.0612 | 0.9182 |
| | N | 9 | 9 | 9 | 10 |
| Mono *1 (%) | Mean | 6.29 | 4.42 | 5.68 | 6.58 |
| | SD | 2.80 | 0.95 | 1.39 | 2.25 |
| | N | 9 | 9 | 9 | 10 |
| Abs Mono ($10^3$/uL) | Mean | 0.3229 | 0.2388 | 0.3100 | 0.3755 |
| | SD | 0.1747 | 0.0717 | 0.1139 | 0.1871 |
| | N | 9 | 9 | 9 | 10 |
| Eosin (%) | Mean | 3.26 | 3.36 | 2.90 | 2.79 |
| | SD | 0.86 | 1.50 | 0.98 | 1.04 |
| | N | 9 | 9 | 9 | 10 |
| Abs Eosin ($10^3$/uL) | Mean | 0.1632 | 0.1736 | 0.1517 | 0.1571 |
| | SD | 0.0698 | 0.0627 | 0.0519 | 0.0750 |
| | N | 9 | 9 | 9 | 10 |
| Baso (%) | Mean | 1.34 | 1.40 | 1.56 | 1.41 |
| | SD | 0.70 | 0.54 | 0.61 | 0.54 |
| | N | 9 | 9 | 9 | 10 |
| Abs Baso ($10^3$/uL) | Mean | 0.0659 | 0.0812 | 0.0883 | 0.0809 |
| | SD | 0.0335 | 0.0507 | 0.0481 | 0.0403 |
| | N | 9 | 9 | 9 | 10 |

*1 - 5% significance level - Group Factor 1 Way ANOVA

# Appendix N

## Clinical Pathology

### TABLE 4: Summary of Hematology Data –Male Rats

Day: 30 Relative to Start Date

| Sex: Male | | Group 1 0mg/kg | Group 2 50mg/kg | Group 3 250mg/kg | Group 4 500mg/kg |
|---|---|---|---|---|---|
| WBC ($10^3$/uL) | Mean | 8.18 | 8.80 | 7.87 | 7.13 |
| | SD | 2.19 | 2.35 | 1.92 | 1.16 |
| | N | 10 | 10 | 10 | 10 |
| RBC *1 ($10^4$/uL) | Mean | 7.462 | 7.682 | 7.362 | 7.320 |
| | SD | 0.280 | 0.261 | 0.271 | 0.279 |
| | N | 10 | 10 | 10 | 10 |
| HGB **2 (g/dL) | Mean | 14.24 | 14.58 | 14.09 | 13.49 **3 |
| | SD | 0.38 | 0.43 | 0.40 | 0.68 |
| | N | 10 | 10 | 10 | 10 |
| HCT **2 (%) | Mean | 41.41 | 42.17 | 41.35 | 39.63 *4 |
| | SD | 0.98 | 1.40 | 1.16 | 1.92 |
| | N | 10 | 10 | 10 | 10 |
| MCV (fL) | Mean | 55.55 | 54.92 | 56.20 | 54.14 |
| | SD | 1.97 | 1.37 | 1.59 | 1.78 |
| | N | 10 | 10 | 10 | 10 |
| MCH **2 (pg) | Mean | 19.12 | 18.97 | 19.17 | 18.41 **3 |
| | SD | 0.46 | 0.40 | 0.57 | 0.47 |
| | N | 10 | 10 | 10 | 10 |
| MCHC (g/dL) | Mean | 34.41 | 34.56 | 34.11 | 34.04 |
| | SD | 0.68 | 0.33 | 0.47 | 0.54 |
| | N | 10 | 10 | 10 | 10 |
| PLT ($10^3$/uL) | Mean | 970.20 | 1015.40 | 908.40 | 937.90 |
| | SD | 65.18 | 101.85 | 137.00 | 161.98 |
| | N | 10 | 10 | 10 | 10 |

*1 - 5% significance level - Group Factor 1 Way ANOVA
**2 - 1% significance level - Group Factor 1 Way ANOVA
**3 - 1% significance level - Dunnett's pairwise comparison
*4 - 5% significance level - Dunnett's pairwise comparison

# Appendix N

## Clinical Pathology

### TABLE 4(continued): Summary of Hematology Data –Male Rats

Day: 30 Relative to Start Date

| Sex: Male | | Group 1 0mg/kg | Group 2 50mg/kg | Group 3 250mg/kg | Group 4 500mg/kg |
|---|---|---|---|---|---|
| Neutro (%) | Mean | 14.72 | 18.14 | 14.72 | 14.00 |
| | SD | 5.19 | 19.61 | 6.38 | 4.43 |
| | N | 10 | 10 | 10 | 10 |
| Abs Neut ($10^3$/uL) | Mean | 1.1668 | 1.9049 | 1.2006 | 0.9903 |
| | SD | 0.4109 | 2.9632 | 0.6824 | 0.3395 |
| | N | 10 | 10 | 10 | 10 |
| Lymph (%) | Mean | 77.56 | 74.56 | 77.00 | 78.39 |
| | SD | 5.24 | 20.03 | 7.30 | 5.52 |
| | N | 10 | 10 | 10 | 10 |
| Abs Lymph ($10^3$/uL) | Mean | 6.3860 | 6.2580 | 6.0170 | 5.6020 |
| | SD | 2.0440 | 1.8431 | 1.4169 | 1.1274 |
| | N | 10 | 10 | 10 | 10 |
| Mono (%) | Mean | 5.34 | 4.91 | 5.86 | 5.50 |
| | SD | 2.07 | 1.94 | 1.45 | 2.82 |
| | N | 10 | 10 | 10 | 10 |
| Abs Mono ($10^3$/uL) | Mean | 0.4237 | 0.4386 | 0.4591 | 0.3746 |
| | SD | 0.1938 | 0.2266 | 0.1712 | 0.1811 |
| | N | 10 | 10 | 10 | 10 |
| Eosin (%) | Mean | 1.62 | 1.67 | 1.62 | 1.49 |
| | SD | 0.57 | 0.73 | 0.64 | 0.57 |
| | N | 10 | 10 | 10 | 10 |
| Abs Eosin ($10^3$/uL) | Mean | 0.1270 | 0.1389 | 0.1331 | 0.1064 |
| | SD | 0.0422 | 0.0491 | 0.0795 | 0.0440 |
| | N | 10 | 10 | 10 | 10 |
| Baso (%) | Mean | 0.76 | 0.68 | 0.83 | 0.60 |
| | SD | 0.41 | 0.34 | 0.41 | 0.51 |
| | N | 10 | 10 | 10 | 10 |
| Abs Baso ($10^3$/uL) | Mean | 0.0625 | 0.0606 | 0.0624 | 0.0408 |
| | SD | 0.0355 | 0.0326 | 0.0287 | 0.0294 |
| | N | 10 | 10 | 10 | 10 |

# Appendix N

## Clinical Pathology

### TABLE 5: Summary of Prothrombin Times –Female Rats

Day: 29 Relative to Start Date

| Sex: Female | | Group 1 0mg/kg | Group 2 50mg/kg | Group 3 250mg/kg | Group 4 500mg/kg |
|---|---|---|---|---|---|
| Prothrombin Time (Seconds) ** 1 | Mean | 13.98 | 13.96 | 13.20 ** 2 | 13.09 ** 2 |
| | SD | 0.49 | 0.37 | 0.37 | 0.50 |
| | N | 9 | 9 | 9 | 10 |

** 1 - 1% significance level - Group Factor 1 Way ANOVA
** 2 - 1% significance level - Dunnett's pairwise comparison

# Appendix N

## TABLE 6: Summary of Prothrombin Times –Male Rats

Day: 30 Relative to Start Date

| Sex: Male | | Group 1<br>0mg/kg | Group 2<br>50mg/kg | Group 3<br>250mg/kg | Group 4<br>500mg/kg |
|---|---|---|---|---|---|
| Prothrombin ** 1 Time (Seconds) | Mean | 14.13 | 14.06 | 14.81 ** 2 | 15.86 ** 2 |
| | SD | 0.49 | 0.42 | 1.10 | 1.36 |
| | N | 10 | 10 | 10 | 10 |

** 1 - 1% significance level - Group Factor 1 Way ANOVA
** 2 - 1% significance level - Dunnett's pairwise comparison

# Appendix N

## Clinical Pathology

### TABLE 7: Abbreviations- Clinical Chemistry

| Heading | Description |
|---|---|
| ***Measurement Descriptions*** | |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| TBILI | Total bilirubin |
| ALB | Albumin |
| TP | Total protein |
| BUN | Blood Urea Nitrogen |
| CREAT | Creatinine |
| GLUC | Glucose |
| CHOL | Cholesterol |
| CA | Calcium |
| PHOS | Phosphate (phosphorus) |
| NA | Sodium |
| K | Potassium |
| CL | Chloride |
| ***Unit Descriptions*** | |
| g/dL | grams/deciliter |
| mg/dL | milligrams/deciliter |
| mmol/L | millimole/liter |
| U/L | unit/liter |

# Appendix N

## Clinical Pathology

### TABLE 8: Abbreviations- Hematology

| Heading | Description |
|---|---|
| ***Measurement Descriptions*** | |
| WBC | White blood cell |
| RBC | Red blood cell |
| PLT | Platelet |
| HGB | Hemoglobin |
| HCT | Hematocrit |
| MCV | Mean Cell Volume |
| MCH | Mean Cell Hemoglobin |
| MCHC | Mean Cell Hemoglobin Concentration |
| ***Unit Descriptions*** | |
| $10^3/\mu L$ | Thousand per microliter |
| $10^6/\mu L$ | Million per microliter |
| % | Percent |
| g | Grams |
| fL | Femtoliter |
| pg | Picogram |

# Appendix N

## Clinical Pathology

### ATTACHMENT 1 - Clinical Chemistry Methodologies

| | Method | Unit | Reference |
|---|---|---|---|
| Albumin | BCG (bromcresol green) | g/dL | Doumas BT, et al, Clin Chim Acta. 1971;31:87-91 |
| Total Protein | biuret | g/dL | Doumas BT, et al, Clin Chem. 1981;27:1642-1654 |
| Glucose | hexokinase | mg/dL | Neely WE. Et al. Clin Chem. 1972;18:509-515 |
| Cholesterol | enzymatic-(cholesterol oxidase) | mg/dL | Allain CC, et al, Clin Chem. 1974;20:470-475 |
| Total Bilirubin | diazo | mg/dL | Malloy, HT, J Biol Chem. 1937;119:481-490 |
| Calcium | o-creolphtalein complex | mg/dL | Schwarzenbach, G. Analyst 1955;80:713-729 |
| Phosphate (Inorganic) | phosphomolybdate, direct | mg/dL | Daly, JS, et al, Clin Chem, 1972;18:263-265 |
| Creatinine | Jaffe-kinetic | mg/dL | Fabiny DL, Clin Chem. 1971;32:81-85 |
| Urea/BUN | urease-kinetic | mg/dL | Sampson EJ, et al, Clin chem. 1980;26:816-826 |
| Alanine Aminotransferase | IFCC/wo pyridoxal phosphate activation | U/L | Bergmeyer HU, et al, J Clin Chem Clin Biochem. 1986;24:481-495 |
| Aspartate Aminotransferase | IFCC/wo pyridoxal phosphate activation | U/L | Bergmeyer HU, et al, J Clin Chem Clin Biochem. 1986;24:497-510 |
| Alkaline Phosphatase | IFCC | U/L | Tietz NW, et al, J Clin Chem Clin Biochem. 1983;21:731-748 |
| Sodium | ISE-indirect | mmol/L | _____ |
| Potassium | ISE-indirect | mmol/L | _____ |
| Chloride | ISE-indirect | mmol/L | _____ |

# Appendix N

## Clinical Pathology

### ATTACHMENT 1 - Hematology Methodologies

| Parameter | Abbreviation | Method | Units |
|---|---|---|---|
| White Blood Cell | WBC | impedance (WIC) | # x $10^3/\mu L$ |
| | | optical (WOC) -flow cytometry | # x $10^3/\mu L$ |
| WBC Differential | %Diff | optical -flow cytometry | % |
| | AbsDiff | calculation | # x $10^3/\mu L$ |
| Red Blood Cell | RBC | impedance | # x $10^6/\mu L$ |
| Platelet | PLT | impedance | # x $10^3/\mu L$ |
| Hemoglobin | HGB | colorimetry | grams (g)/dL |
| Hematocrit | HCT | calculated (RBC x MCV) / 10 | percent (%) |
| Mean Cell Volume | MCV | derived | femtoliters (fL) |
| Mean Cell Hemoglobin | MCH | calculated (HGB/RBC) x 10 | picograms (pg) |
| Mean Cell Hemoglobin Concentration | MCHC | calculated (HGB/HCT) x 100 | percent (%) |

# Appendix N

## Clinical Pathology

## ATTACHMENT 2

## INDIVIDUAL CLINICAL PATHOLOGY DATA

# Appendix N

## Clinical Pathology

## ATTACHMENT 2(continued) : Individual Clinical Chemistry -Female

Day: 29 relative to Start Date

| Group | Sex | Animal | ALP U/L | AST U/L | ALT U/L | TBILI mg/dL | ALB g/dL | TP g/dL | BUN mg/dL | CREAT mg/dL |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | f | 5474 | .* | .* | .* | .* | .* | .* | .* | .* |
| | | 5475 | 110 | 66 | 16 | 0.16 | 4.0 | 6.0 | 15 | 0.4 |
| | | 5476 | 95 | 49 | 19 | 0.09 | 4.2 | 5.9 | 13 | 0.3 |
| | | 5477 | 86 | 64 | 17 | 0.11 | 4.0 | 6.1 | 17 | 0.4 |
| | | 5478 | 102 | 67 | 28 | 0.16 | 4.1 | 6.2 | 17 | 0.3 |
| | | 5479 | 59 | 66 | 24 | 0.10 | 4.2 | 6.2 | 12 | 0.3 |
| | | 5480 | 64 | 49 | 16 | 0.11 | 4.3 | 6.3 | 9 | 0.3 |
| | | 5481 | 87 | 67 | 17 | 0.14 | 3.9 | 6.0 | 14 | 0.3 |
| | | 5482 | 66 | 54 | 16 | 0.12 | 3.7 | 5.4 | 11 | 0.3 |
| | | 5483 | 77 | 64 | 20 | 0.13 | 4.1 | 6.1 | 11 | 0.4 |
| | | Mean | 82.9 | 60.7 | 19.2 | 0.124 | 4.06 | 6.02 | 13.2 | 0.33 |
| | | S.D. | 17.8 | 7.7 | 4.2 | 0.025 | 0.16 | 0.26 | 2.8 | 0.05 |
| | | N | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |

| Group | Sex | Animal | GLUC mg/dL | CHOL mg/dL | CA mg/dL | PHOS mg/dL | CL mmol/L | K mmol/L | NA mmol/L |
|---|---|---|---|---|---|---|---|---|---|
| 1 | f | 5474 | .* | .* | .* | .* | .* | .* | .* |
| | | 5475 | 147 | 48 | 9.4 | 6.0 | 106 | 4.0 | 140 |
| | | 5476 | 146 | 54 | 9.8 | 6.7 | 106 | 4.0 | 140 |
| | | 5477 | 122 | 52 | 9.7 | 7.0 | 103 | 4.2 | 139 |
| | | 5478 | 125 | 50 | 10.0 | 7.7 | 103 | 4.2 | 139 |
| | | 5479 | 133 | 54 | 10.2 | 7.0 | 104 | 4.2 | 140 |
| | | 5480 | 147 | 70 | 10.3 | 8.0 | 102 | 4.3 | 139 |
| | | 5481 | 134 | 61 | 10.0 | 7.9 | 103 | 4.3 | 140 |
| | | 5482 | 116 | 61 | 9.6 | 6.4 | 105 | 3.9 | 141 |
| | | 5483 | 151 | 57 | 9.7 | 6.4 | 105 | 3.9 | 140 |
| | | Mean | 135.7 | 56.3 | 9.86 | 7.01 | 104.1 | 4.11 | 139.8 |
| | | S.D. | 12.7 | 6.8 | 0.29 | 0.72 | 1.5 | 0.16 | 0.7 |
| | | N | 9 | 9 | 9 | 9 | 9 | 9 | 9 |

* = Sample clotted at collection

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix N

## Clinical Pathology

### ATTACHMENT 2(continued) : Individual Clinical Chemistry -Female

Day: 29 relative to Start Date

| Group | Sex | Animal | ALP U/L | AST U/L | ALT U/L | TBILI mg/dL | ALB g/dL | TP g/dL | BUN mg/dL | CREAT mg/dL |
|---|---|---|---|---|---|---|---|---|---|---|
| 2 | f | 5505 | 66 | 86 | 22 | 0.16 | 4.6 | 6.7 | 17 | 0.4 |
| | | 5506 | 94 | 86 | 23 | 0.15 | 3.9 | 5.4 | 15 | 0.3 |
| | | 5507 | 84 | 80 | 25 | 0.13 | 4.2 | 5.9 | 12 | 0.3 |
| | | 5508 | 61 | 69 | 24 | 0.14 | 4.0 | 5.6 | 12 | 0.3 |
| | | 5509 | 112 | 90 | 15 | 0.11 | 4.1 | 5.5 | 15 | 0.4 |
| | | 5510 | 68 | 73 | 15 | 0.12 | 4.0 | 5.9 | 10 | 0.3 |
| | | 5511 | 67 | 64 | 18 | 0.14 | 4.4 | 6.3 | 13 | 0.2 |
| | | 5512 | 64 | 68 | 18 | 0.10 | 4.1 | 5.9 | 11 | 0.3 |
| | | 5513 | 60 | 68 | 17 | 0.14 | 4.1 | 5.7 | 15 | 0.4 |
| | | Mean | 75.1 | 76.0 | 19.7 | 0.132 | 4.16 | 5.88 | 13.3 | 0.32 |
| | | S.D. | 17.8 | 9.6 | 3.9 | 0.019 | 0.22 | 0.41 | 2.3 | 0.07 |
| | | N | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |

| Group | Sex | Animal | GLUC mg/dL | CHOL mg/dL | CA mg/dL | PHOS mg/dL | CL mmol/L | K mmol/L | NA mmol/L |
|---|---|---|---|---|---|---|---|---|---|
| 2 | f | 5505 | 138 | 71 | 10.2 | 6.3 | 103 | 4.4 | 139 |
| | | 5506 | 139 | 59 | 9.6 | 7.1 | 107 | 4.5 | 142 |
| | | 5507 | 138 | 58 | 10.1 | 7.1 | 103 | 3.9 | 140 |
| | | 5508 | 131 | 58 | 9.7 | 6.7 | 104 | 4.2 | 141 |
| | | 5509 | 103 | 33 | 9.2 | 8.0 | 104 | 3.9 | 139 |
| | | 5510 | 117 | 81 | 10.2 | 7.9 | 104 | 4.0 | 142 |
| | | 5511 | 143 | 48 | 10.1 | 7.0 | 102 | 3.8 | 141 |
| | | 5512 | 128 | 54 | 9.6 | 6.6 | 103 | 4.0 | 138 |
| | | 5513 | 110 | 52 | 9.7 | 6.6 | 104 | 4.3 | 139 |
| | | Mean | 127.4 | 57.1 | 9.82 | 7.03 | 103.8 | 4.11 | 140.1 |
| | | S.D. | 14.2 | 13.6 | 0.35 | 0.58 | 1.4 | 0.25 | 1.5 |
| | | N | 9 | 9 | 9 | 9 | 9 | 9 | 9 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix N

## Clinical Pathology

## ATTACHMENT 2(continued) : Individual Clinical Chemistry –Female

Day: 29 relative to Start Date

| Group | Sex | Animal | ALP U/L | AST U/L | ALT U/L | TBILI mg/dL | ALB g/dL | TP g/dL | BUN mg/dL | CREAT mg/dL |
|---|---|---|---|---|---|---|---|---|---|---|
| 3 | f | 5534 | 64 | 79 | 27 | 0.07 | 4.1 | 5.8 | 16 | 0.4 |
| | | 5535 | 63 | 71 | 18 | 0.08 | 3.5 | 5.4 | 17 | 0.3 |
| | | 5536 | 44 | 64 | 16 | 0.08 | 4.6 | 6.4 | 16 | 0.3 |
| | | 5537 | 54 | 90 | 31 | 0.10 | 4.2 | 6.3 | 16 | 0.3 |
| | | 5538 | 87 | 76 | 25 | 0.14 | 4.1 | 6.1 | 12 | 0.3 |
| | | 5539 | 53 | 58 | 22 | 0.08 | 3.6 | 5.7 | 10 | 0.3 |
| | | 5540 | 87 | 58 | 18 | 0.12 | 4.0 | 5.9 | 17 | 0.3 |
| | | 5541 | 34 | 50 | 18 | 0.09 | 4.5 | 6.4 | 12 | 0.3 |
| | | 5542 | 53 | 79 | 21 | 0.07 | 4.1 | 6.0 | 14 | 0.4 |
| | | 5543 | 49 | 56 | 24 | 0.09 | 3.9 | 6.3 | 12 | 0.4 |
| | | Mean | 58.8 | 68.1 | 22.0 | 0.092 | 4.06 | 6.03 | 14.2 | 0.33 |
| | | S.D. | 17.2 | 12.8 | 4.8 | 0.023 | 0.34 | 0.33 | 2.5 | 0.05 |
| | | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

| Group | Sex | Animal | GLUC mg/dL | CHOL mg/dL | CA mg/dL | PHOS mg/dL | CL mmol/L | K mmol/L | NA mmol/L |
|---|---|---|---|---|---|---|---|---|---|
| 3 | f | 5534 | 122 | 44 | 9.6 | 5.8 | 105 | 3.9 | 141 |
| | | 5535 | 123 | 41 | 9.2 | 6.7 | 102 | 4.3 | 136 |
| | | 5536 | 120 | 61 | 10.1 | 7.3 | 104 | 4.4 | 142 |
| | | 5537 | 107 | 64 | 9.9 | 7.5 | 104 | 4.0 | 141 |
| | | 5538 | 146 | 59 | 10.3 | 6.6 | 103 | 4.0 | 139 |
| | | 5539 | 135 | 65 | 9.4 | 6.8 | 104 | 4.0 | 139 |
| | | 5540 | 147 | 77 | 9.8 | 6.5 | 102 | 4.1 | 139 |
| | | 5541 | 132 | 73 | 10.1 | 6.2 | 103 | 3.9 | 140 |
| | | 5542 | 112 | 67 | 9.6 | 6.4 | 104 | 4.0 | 140 |
| | | 5543 | 100 | 74 | 9.9 | 6.3 | 104 | 4.1 | 139 |
| | | Mean | 124.4 | 62.5 | 9.79 | 6.61 | 103.5 | 4.07 | 139.6 |
| | | S.D. | 15.7 | 12.0 | 0.34 | 0.50 | 1.0 | 0.16 | 1.6 |
| | | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix N

## Clinical Pathology

### ATTACHMENT 2(continued): Individual Clinical Chemistry -Female

Day: 29 relative to Start Date

| Group | Sex | Animal | ALP U/L | AST U/L | ALT U/L | TBILI mg/dL | ALB g/dL | TP g/dL | BUN mg/dL | CREAT mg/dL |
|---|---|---|---|---|---|---|---|---|---|---|
| 4 | f | 5564 | 46 | 57 | 34 | 0.07 | 3.7 | 6.3 | 17 | 0.4 |
| | | 5565 | 50 | 50 | 26 | 0.07 | 3.7 | 5.8 | 19 | 0.3 |
| | | 5566 | 74 | 58 | 23 | 0.09 | 3.9 | 6.5 | 15 | 0.4 |
| | | 5567 | 53 | 65 | 32 | 0.16 | 4.0 | 6.6 | 15 | 0.3 |
| | | 5568 | 68 | 50 | 32 | 0.11 | 4.3 | 6.6 | 17 | 0.3 |
| | | 5569 | 37 | 45 | 25 | 0.05 | 4.1 | 6.6 | 13 | 0.2 |
| | | 5570 | 40 | 91 | 22 | 0.12 | 3.8 | 6.4 | 14 | 0.3 |
| | | 5571 | 38 | 53 | 23 | 0.07 | 3.6 | 6.4 | 18 | 0.4 |
| | | 5572 | 49 | 79 | 31 | 0.08 | 3.6 | 6.1 | 16 | 0.4 |
| | | 5573 | 28 | 45 | 21 | 0.06 | 3.9 | 6.4 | 13 | 0.3 |
| | | Mean | 48.3 | 59.3 | 26.9 | 0.088 | 3.86 | 6.37 | 15.7 | 0.33 |
| | | S.D. | 14.1 | 15.1 | 4.9 | 0.033 | 0.23 | 0.25 | 2.1 | 0.07 |
| | | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

| Group | Sex | Animal | GLUC mg/dL | CHOL mg/dL | CA mg/dL | PHOS mg/dL | CL mmol/L | K mmol/L | NA mmol/L |
|---|---|---|---|---|---|---|---|---|---|
| 4 | f | 5564 | 120 | 96 | 10.1 | 5.8 | 101 | 3.8 | 138 |
| | | 5565 | 118 | 76 | 10.0 | 6.4 | 104 | 3.7 | 140 |
| | | 5566 | 131 | 80 | 9.8 | 6.1 | 105 | 4.0 | 140 |
| | | 5567 | 115 | 99 | 9.9 | 6.7 | 101 | 4.3 | 138 |
| | | 5568 | 139 | 87 | 10.4 | 7.1 | 104 | 3.8 | 139 |
| | | 5569 | 127 | 103 | 10.2 | 6.6 | 102 | 3.9 | 139 |
| | | 5570 | 123 | 74 | 9.8 | 7.1 | 102 | 4.0 | 139 |
| | | 5571 | 121 | 81 | 10.0 | 6.8 | 103 | 4.2 | 138 |
| | | 5572 | 113 | 74 | 9.4 | 5.5 | 104 | 4.1 | 138 |
| | | 5573 | 141 | 87 | 9.6 | 5.6 | 102 | 4.1 | 136 |
| | | Mean | 124.8 | 85.7 | 9.92 | 6.37 | 102.8 | 3.99 | 138.5 |
| | | S.D. | 9.6 | 10.6 | 0.29 | 0.59 | 1.4 | 0.19 | 1.2 |
| | | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix N

## Clinical Pathology

## ATTACHMENT 2 (continued): Individual Clinical Chemistry -Male

Day: 30 relative to Start Date

| Group | Sex | Animal | ALP U/L | AST U/L | ALT U/L | TBILI mg/dL | ALB g/dL | TP g/dL | BUN mg/dL | CREAT mg/dL |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | m | 5484 | 227 | 86 | 16 | 0.17 | 3.8 | 5.6 | 11 | 0.3 |
| | | 5485 | 132 | 82 | 25 | 0.12 | 3.9 | 5.7 | 12 | 0.3 |
| | | 5486 | 131 | 90 | 18 | 0.11 | 3.9 | 5.9 | 11 | 0.3 |
| | | 5487 | 111 | 106 | 17 | 0.08 | 3.6 | 5.8 | 13 | 0.3 |
| | | 5488 | 111 | 109 | 20 | 0.18 | 3.8 | 6.0 | 11 | 0.3 |
| | | 5489 | 147 | 82 | 15 | 0.11 | 3.8 | 5.7 | 9 | 0.3 |
| | | 5490 | 111 | 76 | 16 | 0.13 | 3.6 | 5.6 | 11 | 0.3 |
| | | 5491 | 211 | 79 | 16 | 0.11 | 3.6 | 5.6 | 12 | 0.4 |
| | | 5492 | 110 | 83 | 20 | 0.11 | 3.4 | 5.2 | 13 | 0.3 |
| | | 5493 | 116 | 62 | 13 | 0.10 | 3.8 | 5.8 | 10 | 0.3 |
| | | Mean | 140.7 | 85.5 | 17.6 | 0.122 | 3.72 | 5.69 | 11.3 | 0.31 |
| | | S.D. | 43.2 | 13.8 | 3.4 | 0.031 | 0.16 | 0.22 | 1.3 | 0.03 |
| | | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

| Group | Sex | Animal | GLUC mg/dL | CHOL mg/dL | CA mg/dL | PHOS mg/dL | CL mmol/L | K mmol/L | NA mmol/L |
|---|---|---|---|---|---|---|---|---|---|
| 1 | m | 5484 | 146 | 51 | 9.9 | 7.0 | 104 | 4.3 | 142 |
| | | 5485 | 136 | 28 | 9.5 | 7.2 | 103 | 4.1 | 142 |
| | | 5486 | 138 | 61 | 9.6 | 7.1 | 102 | 4.5 | 140 |
| | | 5487 | 128 | 41 | 10.3 | 8.3 | 103 | 4.4 | 143 |
| | | 5488 | 127 | 52 | 10.1 | 8.5 | 100 | 4.7 | 141 |
| | | 5489 | 147 | 68 | 10.1 | 7.9 | 102 | 4.6 | 142 |
| | | 5490 | 140 | 41 | 9.9 | 7.9 | 103 | 4.6 | 141 |
| | | 5491 | 145 | 49 | 9.5 | 8.1 | 103 | 4.7 | 141 |
| | | 5492 | 138 | 36 | 9.2 | 6.9 | 105 | 4.3 | 141 |
| | | 5493 | 121 | 51 | 9.7 | 6.9 | 103 | 4.8 | 141 |
| | | Mean | 136.6 | 47.8 | 9.78 | 7.58 | 102.8 | 4.50 | 141.4 |
| | | S.D. | 8.8 | 11.8 | 0.34 | 0.62 | 1.3 | 0.22 | 0.8 |
| | | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix N

## Clinical Pathology

## ATTACHMENT 2(continued): Individual Clinical Chemistry -Male

Day: 30 relative to Start Date

| Group | Sex | Animal | ALP U/L | AST U/L | ALT U/L | TBILI mg/dL | ALB g/dL | TP g/dL | BUN mg/dL | CREAT mg/dL |
|---|---|---|---|---|---|---|---|---|---|---|
| 2 | m | 5514 | 168 | 75 | 29 | 0.11 | 3.9 | 6.1 | 11 | 0.3 |
| | | 5515 | 120 | 52 | 18 | 0.11 | 3.7 | 5.6 | 13 | 0.3 |
| | | 5516 | 142 | 72 | 23 | 0.09 | 3.7 | 5.6 | 13 | 0.3 |
| | | 5517 | 134 | 78 | 26 | 0.10 | 3.7 | 5.9 | 12 | 0.2 |
| | | 5518 | 102 | 79 | 19 | 0.09 | 3.5 | 5.8 | 8 | 0.3 |
| | | 5519 | 179 | 55 | 20 | 0.11 | 3.7 | 5.9 | 14 | 0.3 |
| | | 5520 | 114 | 65 | 21 | 0.13 | 3.6 | 5.9 | 12 | 0.3 |
| | | 5521 | 111 | 69 | 17 | 0.10 | 3.8 | 5.9 | 11 | 0.3 |
| | | 5522 | 156 | 65 | 21 | 0.10 | 3.7 | 5.5 | 13 | 0.3 |
| | | 5523 | 107 | 98 | 21 | 0.09 | 3.6 | 5.6 | 15 | 0.3 |
| | | Mean | 133.3 | 70.8 | 21.5 | 0.103 | 3.69 | 5.78 | 12.2 | 0.29 |
| | | S.D. | 27.1 | 13.1 | 3.7 | 0.013 | 0.11 | 0.19 | 1.9 | 0.03 |
| | | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

| Group | Sex | Animal | GLUC mg/dL | CHOL mg/dL | CA mg/dL | PHOS mg/dL | CL mmol/L | K mmol/L | NA mmol/L |
|---|---|---|---|---|---|---|---|---|---|
| 2 | m | 5514 | 151 | 49 | 9.7 | 7.1 | 102 | 4.4 | 141 |
| | | 5515 | 136 | 46 | 9.9 | 7.1 | 101 | 4.5 | 140 |
| | | 5516 | 131 | 32 | 9.5 | 7.3 | 101 | 4.3 | 139 |
| | | 5517 | 151 | 57 | 10.2 | 8.7 | 102 | 4.3 | 142 |
| | | 5518 | 106 | 37 | 9.8 | 8.2 | 102 | 4.3 | 142 |
| | | 5519 | 144 | 42 | 10.3 | 8.1 | 102 | 4.3 | 142 |
| | | 5520 | 145 | 48 | 9.9 | 7.5 | 102 | 4.6 | 141 |
| | | 5521 | 128 | 64 | 9.6 | 7.1 | 102 | 4.1 | 141 |
| | | 5522 | 163 | 31 | 10.1 | 8.0 | 104 | 4.7 | 141 |
| | | 5523 | 133 | 40 | 9.5 | 7.8 | 102 | 4.8 | 139 |
| | | Mean | 138.8 | 44.6 | 9.85 | 7.69 | 102.0 | 4.43 | 140.8 |
| | | S.D. | 15.8 | 10.5 | 0.28 | 0.56 | 0.8 | 0.22 | 1.1 |
| | | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix N

## Clinical Pathology

## ATTACHMENT 2 (continued): Individual Clinical Chemistry -Male

Day: 30 relative to Start Date

| Group | Sex | Animal | ALP U/L | AST U/L | ALT U/L | TBILI mg/dL | ALB g/dL | TP g/dL | BUN mg/dL | CREAT mg/dL |
|---|---|---|---|---|---|---|---|---|---|---|
| 3 | m | 5544 | 83 | 56 | 21 | 0.08 | 3.6 | 6.1 | 11 | 0.3 |
| | | 5545 | 121 | 53 | 27 | 0.06 | 3.6 | 5.8 | 15 | 0.3 |
| | | 5546 | 113 | 63 | 23 | 0.08 | 3.5 | 6.0 | 10 | 0.3 |
| | | 5547 | 94 | 56 | 22 | 0.08 | 3.6 | 5.6 | 12 | 0.3 |
| | | 5548 | 147 | 79 | 23 | 0.11 | 3.5 | 5.6 | 16 | 0.2 |
| | | 5549 | 88 | 46 | 16 | 0.08 | 3.6 | 5.8 | 12 | 0.3 |
| | | 5550 | 76 | 62 | 21 | 0.11 | 3.6 | 5.8 | 15 | 0.3 |
| | | 5551 | 90 | 56 | 17 | 0.10 | 3.5 | 5.4 | 14 | 0.3 |
| | | 5552 | 103 | 54 | 17 | 0.07 | 3.7 | 5.6 | 14 | 0.3 |
| | | 5553 | 85 | 55 | 18 | 0.09 | 3.5 | 5.3 | 12 | 0.3 |
| | | Mean | 100.0 | 58.0 | 20.5 | 0.086 | 3.57 | 5.70 | 13.1 | 0.29 |
| | | S.D. | 21.6 | 8.7 | 3.5 | 0.016 | 0.07 | 0.25 | 2.0 | 0.03 |
| | | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

| Group | Sex | Animal | GLUC mg/dL | CHOL mg/dL | CA mg/dL | PHOS mg/dL | CL mmol/L | K mmol/L | NA mmol/L |
|---|---|---|---|---|---|---|---|---|---|
| 3 | m | 5544 | 163 | 41 | 9.9 | 7.2 | 103 | 4.8 | 141 |
| | | 5545 | 147 | 34 | 9.7 | 6.7 | 102 | 4.2 | 140 |
| | | 5546 | 144 | 52 | 10.0 | 7.8 | 102 | 4.5 | 140 |
| | | 5547 | 155 | 51 | 10.1 | 8.7 | 103 | 4.4 | 141 |
| | | 5548 | 119 | 43 | 10.1 | 8.0 | 103 | 4.8 | 141 |
| | | 5549 | 165 | 50 | 10.1 | 7.9 | 102 | 4.3 | 141 |
| | | 5550 | 104 | 41 | 9.5 | 6.6 | 102 | 4.2 | 140 |
| | | 5551 | 156 | 64 | 9.6 | 7.4 | 104 | 4.8 | 141 |
| | | 5552 | 127 | 34 | 9.9 | 7.6 | 104 | 4.6 | 142 |
| | | 5553 | 138 | 47 | 9.6 | 7.1 | 105 | 4.3 | 141 |
| | | Mean | 141.8 | 45.7 | 9.85 | 7.60 | 103.0 | 4.49 | 140.8 |
| | | S.D. | 19.9 | 9.1 | 0.23 | 0.79 | 1.1 | 0.25 | 0.6 |
| | | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix N

## Clinical Pathology

## ATTACHMENT 2 (continued): Individual Clinical Chemistry -Male

Day: 30 relative to Start Date

| Group | Sex | Animal | ALP U/L | AST U/L | ALT U/L | TBILI mg/dL | ALB g/dL | TP g/dL | BUN mg/dL | CREAT mg/dL |
|---|---|---|---|---|---|---|---|---|---|---|
| 4 | m | 5574 | 86 | 46 | 29 | 0.06 | 3.7 | 5.9 | 13 | 0.3 |
| | | 5575 | 134 | 47 | 26 | 0.12 | 3.8 | 6.2 | 13 | 0.3 |
| | | 5576 | 75 | 47 | 49 | 0.11 | 3.5 | 5.8 | 14 | 0.3 |
| | | 5577 | 110 | 47 | 20 | 0.07 | 3.4 | 5.7 | 11 | 0.2 |
| | | 5578 | 77 | 56 | 28 | 0.08 | 3.6 | 6.0 | 14 | 0.3 |
| | | 5579 | 85 | 55 | 26 | 0.12 | 3.6 | 5.9 | 15 | 0.3 |
| | | 5580 | 87 | 51 | 26 | 0.08 | 3.6 | 6.0 | 18 | 0.3 |
| | | 5581 | 90 | 54 | 26 | 0.07 | 3.6 | 5.9 | 16 | 0.3 |
| | | 5582 | 97 | 40 | 22 | 0.06 | 3.7 | 5.9 | 17 | 0.2 |
| | | 5583 | 57 | 45 | 19 | 0.07 | 3.7 | 6.1 | 13 | 0.3 |
| | | Mean | 89.8 | 48.8 | 27.1 | 0.084 | 3.62 | 5.94 | 14.4 | 0.28 |
| | | S.D. | 20.9 | 5.1 | 8.4 | 0.024 | 0.11 | 0.14 | 2.1 | 0.04 |
| | | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

| Group | Sex | Animal | GLUC mg/dL | CHOL mg/dL | CA mg/dL | PHOS mg/dL | CL mmol/L | K mmol/L | NA mmol/L |
|---|---|---|---|---|---|---|---|---|---|
| 4 | m | 5574 | 154 | 30 | 9.7 | 6.4 | 103 | 3.9 | 140 |
| | | 5575 | 143 | 47 | 10.0 | 6.9 | 103 | 4.3 | 141 |
| | | 5576 | 141 | 66 | 9.7 | 7.1 | 106 | 4.6 | 139 |
| | | 5577 | 156 | 47 | 10.0 | 8.1 | 103 | 4.5 | 141 |
| | | 5578 | 141 | 51 | 9.8 | 7.8 | 103 | 4.7 | 140 |
| | | 5579 | 137 | 67 | 9.9 | 6.9 | 101 | 4.3 | 139 |
| | | 5580 | 146 | 44 | 10.4 | 7.7 | 102 | 4.6 | 140 |
| | | 5581 | 123 | 55 | 9.8 | 7.1 | 101 | 4.4 | 138 |
| | | 5582 | 146 | 31 | 10.3 | 7.1 | 104 | 4.3 | 140 |
| | | 5583 | 148 | 48 | 10.4 | 6.9 | 103 | 4.7 | 140 |
| | | Mean | 143.5 | 48.6 | 10.00 | 7.20 | 102.9 | 4.43 | 139.8 |
| | | S.D. | 9.3 | 12.3 | 0.27 | 0.51 | 1.4 | 0.25 | 0.9 |
| | | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix N

## Clinical Pathology

## ATTACHMENT 2(continued): Individual Hematology -Female

Day: 29 relative to Start Date

| Group | Sex | Animal | WBC 10^3/uL | RBC 10^6/uL | HGB g/dL | HCT % | MCV fL | MCH pg | MCHC g/dL | PLT 10^3/uL | Neutro % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | f | 5474 | .* | .* | .* | .* | .* | .* | .* | .* | .* |
| | | 5475 | 3.5 | 7.13 | 13.8 | 40.7 | 57.1 | 19.3 | 33.9 | 1284.0 | 29.0 |
| | | 5476 | 3.7 | 7.43 | 14.4 | 43.3 | 58.3 | 19.4 | 33.2 | 1118.0 | 20.5 |
| | | 5477 | 2.9 | 7.42 | 14.1 | 41.8 | 56.3 | 19.0 | 33.7 | 1216.0 | 19.5 |
| | | 5478 | 8.9 | 6.76 | 14.4 | 43.3 | 64.2 | 21.4 | 33.3 | 1131.0 | 8.6 |
| | | 5479 | 4.3 | 7.68 | 15.0 | 44.1 | 57.4 | 19.5 | 34.0 | 1336.0 | 11.9 |
| | | 5480 | 6.6 | 7.54 | 14.6 | 43.3 | 57.4 | 19.3 | 33.7 | 1175.0 | 15.7 |
| | | 5481 | 5.8 | 7.69 | 15.0 | 44.5 | 56.4 | 19.0 | 33.8 | 1145.0 | 25.3 |
| | | 5482 | 5.0 | 7.29 | 14.7 | 43.0 | 59.0 | 20.2 | 34.3 | 1267.0 | 24.3 |
| | | 5483 | 4.8 | 7.45 | 14.7 | 43.1 | 57.9 | 19.8 | 34.1 | 982.0 | 11.0 |
| | | Mean | 5.06 | 7.399 | 14.52 | 43.01 | 58.22 | 19.66 | 33.78 | 1183.78 | 18.42 |
| | | S.D. | 1.85 | 0.323 | 0.40 | 1.14 | 2.40 | 0.76 | 0.36 | 106.41 | 7.08 |
| | | N | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |

| Group | Sex | Animal | Abs Neut 10^3/uL | Lymph % | Abs Lymph 10^3/uL | Mono % | Abs Mono 10^3/uL | Eosin % | Abs Eosin 10^3/uL | Baso % | Abs Baso 10^3/uL |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | f | 5474 | .* | .* | .* | .* | .* | .* | .* | .* | .* |
| | | 5475 | 1.020 | 60.3 | 2.120 | 5.2 | 0.181 | 3.8 | 0.135 | 1.7 | 0.060 |
| | | 5476 | 0.749 | 60.5 | 2.210 | 12.0 | 0.436 | 4.0 | 0.147 | 2.9 | 0.107 |
| | | 5477 | 0.556 | 74.3 | 2.120 | 2.7 | 0.077 | 2.4 | 0.070 | 1.1 | 0.032 |
| | | 5478 | 0.761 | 79.3 | 7.050 | 7.3 | 0.648 | 3.6 | 0.318 | 1.3 | 0.116 |
| | | 5479 | 0.511 | 80.1 | 3.430 | 3.2 | 0.137 | 4.4 | 0.190 | 0.3 | 0.014 |
| | | 5480 | 1.030 | 75.6 | 4.980 | 5.1 | 0.336 | 2.3 | 0.151 | 1.4 | 0.091 |
| | | 5481 | 1.460 | 64.4 | 3.700 | 6.3 | 0.363 | 3.0 | 0.174 | 0.9 | 0.053 |
| | | 5482 | 1.220 | 64.3 | 3.230 | 8.3 | 0.416 | 2.0 | 0.101 | 1.1 | 0.055 |
| | | 5483 | 0.527 | 77.3 | 3.700 | 6.5 | 0.312 | 3.8 | 0.183 | 1.4 | 0.065 |
| | | Mean | 0.8704 | 70.68 | 3.6156 | 6.29 | 0.3229 | 3.26 | 0.1632 | 1.34 | 0.0659 |
| | | S.D. | 0.3336 | 8.18 | 1.5931 | 2.80 | 0.1747 | 0.86 | 0.0698 | 0.70 | 0.0335 |
| | | N | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |

* = Sample clotted at collection

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix N

## Clinical Pathology

## ATTACHMENT 2 (continued): Individual Hematology -Female

Day: 29 relative to Start Date

| Group | Sex | Animal | WBC 10^3/uL | RBC 10^6/uL | HGB g/dL | HCT % | MCV fL | MCH pg | MCHC g/dL | PLT 10^3/uL | Neutro % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | f | 5505 | 4.3 | 7.02 | 13.8 | 41.3 | 58.9 | 19.7 | 33.5 | 1149.0 | 10.2 |
| | | 5506 | 4.6 | 7.98 | 14.9 | 45.0 | 56.3 | 18.7 | 33.2 | 1254.0 | 10.1 |
| | | 5507 | 4.3 | 7.64 | 14.7 | 43.1 | 56.4 | 19.3 | 34.2 | 1299.0 | 24.0 |
| | | 5508 | 6.8 | 7.40 | 14.9 | 44.4 | 60.0 | 20.1 | 33.6 | 1232.0 | 7.7 |
| | | 5509 | 4.4 | 7.31 | 14.1 | 41.8 | 57.3 | 19.3 | 33.7 | 1025.0 | 15.7 |
| | | 5510 | 6.6 | 6.73 | 14.3 | 42.8 | 63.5 | 21.2 | 33.4 | 1038.0 | 17.2 |
| | | 5511 | 5.5 | 7.60 | 15.0 | 44.2 | 56.6 | 19.3 | 34.0 | 1341.0 | 10.1 |
| | | 5512 | 4.0 | 7.38 | 14.2 | 42.2 | 57.2 | 19.3 | 33.7 | 1131.0 | 9.6 |
| | | 5513 | 8.8 | 7.29 | 14.6 | 43.3 | 59.5 | 20.1 | 33.8 | 1197.0 | 4.0 |
| | | Mean | 5.48 | 7.394 | 14.50 | 43.12 | 58.41 | 19.67 | 33.68 | 1185.11 | 12.07 |
| | | S.D. | 1.62 | 0.382 | 0.42 | 1.24 | 2.35 | 0.72 | 0.30 | 109.47 | 5.95 |
| | | N | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |

| Group | Sex | Animal | Abs Neut 10^3/uL | Lymph % | Abs Lymph 10^3/uL | Mono % | Abs Mono 10^3/uL | Eosin % | Abs Eosin 10^3/uL | Baso % | Abs Baso 10^3/uL |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | f | 5505 | 0.440 | 77.6 | 3.350 | 4.9 | 0.211 | 5.8 | 0.251 | 1.6 | 0.067 |
| | | 5506 | 0.462 | 79.8 | 3.650 | 4.5 | 0.206 | 4.3 | 0.198 | 1.3 | 0.058 |
| | | 5507 | 1.030 | 67.2 | 2.900 | 5.1 | 0.218 | 2.3 | 0.099 | 1.4 | 0.059 |
| | | 5508 | 0.528 | 84.5 | 5.780 | 4.3 | 0.295 | 1.5 | 0.099 | 2.0 | 0.136 |
| | | 5509 | 0.699 | 76.1 | 3.380 | 2.4 | 0.105 | 5.5 | 0.244 | 0.3 | 0.011 |
| | | 5510 | 1.140 | 73.3 | 4.850 | 5.2 | 0.344 | 2.6 | 0.173 | 1.7 | 0.112 |
| | | 5511 | 0.558 | 81.0 | 4.460 | 4.3 | 0.234 | 3.2 | 0.173 | 1.4 | 0.079 |
| | | 5512 | 0.384 | 81.6 | 3.260 | 5.5 | 0.218 | 2.4 | 0.097 | 0.9 | 0.036 |
| | | 5513 | 0.349 | 87.8 | 7.720 | 3.6 | 0.318 | 2.6 | 0.228 | 2.0 | 0.173 |
| | | Mean | 0.6211 | 78.77 | 4.3722 | 4.42 | 0.2388 | 3.36 | 0.1736 | 1.40 | 0.0812 |
| | | S.D. | 0.2836 | 6.13 | 1.5565 | 0.95 | 0.0717 | 1.50 | 0.0627 | 0.54 | 0.0507 |
| | | N | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix N

## Clinical Pathology

## ATTACHMENT 2(continued): Individual Hematology –Female

Day: 29 relative to Start Date

| Group | Sex | Animal | WBC 10^3/uL | RBC 10^6/uL | HGB g/dL | HCT % | MCV fL | MCH pg | MCHC g/dL | PLT 10^3/uL | Neutro % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | f | 5534 | 7.2 | 7.18 | 13.2 | 38.9 | 54.2 | 18.4 | 33.9 | 946.0 | 12.3 |
| | | 5535 | 5.7 | 7.08 | 13.9 | 40.8 | 57.7 | 19.6 | 34.0 | 1361.0 | 11.8 |
| | | 5536 | 3.0 | 7.54 | 14.2 | 42.2 | 55.9 | 18.8 | 33.6 | 1389.0 | 11.9 |
| | | 5537 | 3.7 | 7.35 | 14.4 | 42.7 | 58.1 | 19.6 | 33.7 | 1249.0 | 9.6 |
| | | 5538 | .* | .* | .* | .* | .* | .* | .* | .* | .* |
| | | 5539 | 8.1 | 7.10 | 13.9 | 41.8 | 58.8 | 19.6 | 33.3 | 1219.0 | 24.9 |
| | | 5540 | 4.6 | 7.84 | 14.8 | 45.0 | 57.5 | 18.9 | 32.9 | 880.0 | 8.5 |
| | | 5541 | 4.9 | 7.55 | 14.1 | 41.8 | 55.3 | 18.7 | 33.8 | 1222.0 | 9.4 |
| | | 5542 | 5.8 | 7.86 | 14.3 | 43.2 | 55.0 | 18.2 | 33.1 | 1112.0 | 10.1 |
| | | 5543 | 6.2 | 7.41 | 14.6 | 43.6 | 58.9 | 19.7 | 33.4 | 1260.0 | 26.8 |
| | | Mean | 5.47 | 7.434 | 14.16 | 42.22 | 56.82 | 19.06 | 33.52 | 1182.00 | 13.92 |
| | | S.D. | 1.62 | 0.292 | 0.47 | 1.74 | 1.75 | 0.58 | 0.37 | 173.29 | 6.90 |
| | | N | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |

| Group | Sex | Animal | Abs Neut 10^3/uL | Lymph % | Abs Lymph 10^3/uL | Mono % | Abs Mono 10^3/uL | Eosin % | Abs Eosin 10^3/uL | Baso % | Abs Baso 10^3/uL |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | f | 5534 | 0.884 | 77.9 | 5.570 | 5.3 | 0.377 | 2.3 | 0.166 | 2.2 | 0.157 |
| | | 5535 | 0.667 | 77.2 | 4.370 | 4.6 | 0.261 | 3.8 | 0.214 | 2.6 | 0.149 |
| | | 5536 | 0.360 | 78.4 | 2.370 | 4.1 | 0.123 | 4.4 | 0.134 | 1.2 | 0.035 |
| | | 5537 | 0.356 | 80.6 | 2.990 | 6.2 | 0.231 | 2.4 | 0.090 | 1.2 | 0.045 |
| | | 5538 | .* | .* | .* | .* | .* | .* | .* | .* | .* |
| | | 5539 | 2.020 | 67.4 | 5.460 | 4.7 | 0.383 | 1.6 | 0.132 | 1.3 | 0.107 |
| | | 5540 | 0.386 | 80.6 | 3.670 | 7.0 | 0.317 | 2.8 | 0.127 | 1.1 | 0.051 |
| | | 5541 | 0.460 | 81.2 | 3.990 | 5.9 | 0.290 | 2.7 | 0.130 | 0.9 | 0.044 |
| | | 5542 | 0.583 | 80.9 | 4.680 | 4.8 | 0.277 | 2.0 | 0.117 | 2.2 | 0.128 |
| | | 5543 | 1.670 | 59.3 | 3.690 | 8.5 | 0.531 | 4.1 | 0.255 | 1.3 | 0.079 |
| | | Mean | 0.8207 | 75.94 | 4.0878 | 5.68 | 0.3100 | 2.90 | 0.1517 | 1.56 | 0.0883 |
| | | S.D. | 0.6115 | 7.56 | 1.0612 | 1.39 | 0.1139 | 0.98 | 0.0519 | 0.61 | 0.0481 |
| | | N | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix N

## Clinical Pathology

## ATTACHMENT 2(continued): Individual Hematology -Female

Day: 29 relative to Start Date

| Group | Sex | Animal | WBC 10^3/uL | RBC 10^6/uL | HGB g/dL | HCT % | MCV fL | MCH pg | MCHC g/dL | PLT 10^3/uL | Neutro % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 4 | f | 5564 | 6.3 | 7.33 | 13.6 | 40.8 | 55.7 | 18.6 | 33.3 | 1220.0 | 16.6 |
| | | 5565 | 5.8 | 7.13 | 13.7 | 41.0 | 57.4 | 19.3 | 33.6 | 911.0 | 8.2 |
| | | 5566 | 4.5 | 7.22 | 13.5 | 41.3 | 57.1 | 18.7 | 32.8 | 1102.0 | 31.5 |
| | | 5567 | 4.4 | 7.51 | 13.8 | 41.6 | 55.4 | 18.3 | 33.1 | 1338.0 | 21.5 |
| | | 5568 | 4.4 | 7.21 | 14.3 | 44.0 | 61.0 | 19.8 | 32.5 | 974.0 | 18.5 |
| | | 5569 | 5.7 | 7.32 | 14.1 | 43.0 | 58.7 | 19.3 | 32.8 | 1044.0 | 7.3 |
| | | 5570 | 4.6 | 7.41 | 13.9 | 41.9 | 56.5 | 18.7 | 33.1 | 1109.0 | 12.6 |
| | | 5571 | 9.0 | 7.23 | 13.7 | 41.2 | 57.1 | 18.9 | 33.1 | 1165.0 | 28.2 |
| | | 5572 | 4.9 | 7.34 | 14.1 | 42.2 | 57.5 | 19.3 | 33.5 | 1109.0 | 11.1 |
| | | 5573 | 6.1 | 7.57 | 14.5 | 43.2 | 57.0 | 19.1 | 33.5 | 1158.0 | 7.1 |
| | | Mean | 5.57 | 7.327 | 13.92 | 42.02 | 57.34 | 19.00 | 33.13 | 1113.00 | 16.26 |
| | | S.D. | 1.41 | 0.139 | 0.32 | 1.07 | 1.59 | 0.44 | 0.36 | 121.03 | 8.67 |
| | | N. | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

| Group | Sex | Animal | Abs Neut 10^3/uL | Lymph % | Abs Lymph 10^3/uL | Mono % | Abs Mono 10^3/uL | Eosin % | Abs Eosin 10^3/uL | Baso % | Abs Baso 10^3/uL |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 4 | f | 5564 | 1.050 | 68.9 | 4.360 | 7.8 | 0.492 | 4.9 | 0.309 | 1.9 | 0.120 |
| | | 5565 | 0.477 | 79.4 | 4.600 | 6.7 | 0.386 | 4.2 | 0.244 | 1.5 | 0.085 |
| | | 5566 | 1.430 | 58.3 | 2.640 | 7.3 | 0.330 | 1.6 | 0.072 | 1.3 | 0.059 |
| | | 5567 | 0.944 | 69.0 | 3.020 | 6.0 | 0.263 | 2.2 | 0.096 | 1.3 | 0.058 |
| | | 5568 | 0.815 | 71.5 | 3.140 | 5.5 | 0.240 | 3.4 | 0.148 | 1.2 | 0.052 |
| | | 5569 | 0.415 | 83.1 | 4.730 | 6.1 | 0.348 | 2.2 | 0.125 | 1.3 | 0.076 |
| | | 5570 | 0.572 | 74.1 | 3.370 | 9.2 | 0.419 | 2.1 | 0.094 | 2.0 | 0.091 |
| | | 5571 | 2.540 | 59.3 | 5.330 | 8.5 | 0.767 | 2.3 | 0.209 | 1.6 | 0.146 |
| | | 5572 | 0.540 | 85.3 | 4.170 | 1.1 | 0.051 | 2.5 | 0.122 | 0.1 | 0.006 |
| | | 5573 | 0.433 | 80.9 | 4.910 | 7.6 | 0.459 | 2.5 | 0.152 | 1.9 | 0.116 |
| | | Mean | 0.9216 | 72.98 | 4.0270 | 6.58 | 0.3755 | 2.79 | 0.1571 | 1.41 | 0.0809 |
| | | S.D. | 0.6555 | 9.41 | 0.9182 | 2.25 | 0.1871 | 1.04 | 0.0750 | 0.54 | 0.0403 |
| | | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix N

## Clinical Pathology

## ATTACHMENT 2 : (continued) Individual Hematology -Male

Day: 30 relative to Start Date

| Group | Sex | Animal | WBC 10^3/uL | RBC 10^6/uL | HGB g/dL | HCT % | MCV fL | MCH pg | MCHC g/dL | PLT 10^3/uL | Neutro % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | m | 5484 | 8.1 | 7.20 | 14.0 | 42.2 | 58.7 | 19.5 | 33.3 | 1038.0 | 11.6 |
| | | 5485 | 8.6 | 7.37 | 14.3 | 41.6 | 56.4 | 19.5 | 34.5 | 864.0 | 24.4 |
| | | 5486 | 6.4 | 7.16 | 14.0 | 41.4 | 57.7 | 19.6 | 33.9 | 970.0 | 11.8 |
| | | 5487 | 7.0 | 7.59 | 14.6 | 42.6 | 56.1 | 19.2 | 34.2 | 906.0 | 17.8 |
| | | 5488 | 5.7 | 7.16 | 13.6 | 40.3 | 56.2 | 19.0 | 33.9 | 1065.0 | 14.2 |
| | | 5489 | 12.9 | 7.63 | 14.5 | 42.5 | 55.7 | 19.0 | 34.0 | 966.0 | 8.6 |
| | | 5490 | 9.8 | 8.03 | 14.7 | 42.1 | 52.4 | 18.3 | 34.9 | 962.0 | 14.3 |
| | | 5491 | 9.8 | 7.25 | 14.1 | 40.1 | 55.3 | 19.5 | 35.2 | 1049.0 | 12.6 |
| | | 5492 | 7.4 | 7.56 | 13.9 | 40.0 | 53.0 | 18.4 | 34.7 | 916.0 | 9.8 |
| | | 5493 | 6.1 | 7.65 | 14.7 | 41.3 | 54.0 | 19.2 | 35.5 | 966.0 | 22.1 |
| | | Mean | 8.18 | 7.462 | 14.24 | 41.41 | 55.55 | 19.12 | 34.41 | 970.20 | 14.72 |
| | | S.D. | 2.19 | 0.280 | 0.38 | 0.98 | 1.97 | 0.46 | 0.68 | 65.18 | 5.19 |
| | | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

| Group | Sex | Animal | Abs Neut 10^3/uL | Lymph % | Abs Lymph 10^3/uL | Mono % | Abs Mono 10^3/uL | Eosin % | Abs Eosin 10^3/uL | Baso % | Abs Baso 10^3/uL |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | m | 5484 | 0.945 | 79.0 | 6.420 | 5.7 | 0.467 | 2.0 | 0.165 | 1.7 | 0.134 |
| | | 5485 | 2.100 | 73.0 | 6.260 | 1.1 | 0.097 | 0.8 | 0.071 | 0.6 | 0.049 |
| | | 5486 | 0.755 | 79.9 | 5.120 | 5.3 | 0.338 | 2.2 | 0.142 | 0.9 | 0.055 |
| | | 5487 | 1.250 | 74.1 | 5.180 | 6.2 | 0.433 | 1.1 | 0.076 | 0.8 | 0.056 |
| | | 5488 | 0.805 | 77.9 | 4.410 | 5.7 | 0.325 | 1.7 | 0.096 | 0.4 | 0.024 |
| | | 5489 | 1.110 | 87.4 | 11.200 | 2.4 | 0.305 | 1.2 | 0.150 | 0.5 | 0.065 |
| | | 5490 | 1.400 | 74.8 | 7.340 | 8.1 | 0.795 | 2.0 | 0.199 | 0.8 | 0.083 |
| | | 5491 | 1.230 | 78.4 | 7.660 | 6.8 | 0.661 | 1.2 | 0.112 | 1.1 | 0.103 |
| | | 5492 | 0.723 | 82.4 | 6.080 | 6.1 | 0.449 | 1.4 | 0.100 | 0.3 | 0.023 |
| | | 5493 | 1.350 | 68.7 | 4.190 | 6.0 | 0.367 | 2.6 | 0.159 | 0.5 | 0.033 |
| | | Mean | 1.1668 | 77.56 | 6.3860 | 5.34 | 0.4237 | 1.62 | 0.1270 | 0.76 | 0.0625 |
| | | S.D. | 0.4109 | 5.24 | 2.0440 | 2.07 | 0.1938 | 0.57 | 0.0422 | 0.41 | 0.0355 |
| | | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix N

## Clinical Pathology

## ATTACHMENT 2 (continued): Individual Hematology -Male

Day: 30 relative to Start Date

| Group | Sex | Animal | WBC 10^3/uL | RBC 10^6/uL | HGB g/dL | HCT % | MCV fL | MCH pg | MCHC g/dL | PLT 10^3/uL | Neutro % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | m | 5514 | 10.2 | 8.04 | 15.3 | 44.5 | 55.4 | 19.0 | 34.4 | 894.0 | 15.0 |
| | | 5515 | 7.3 | 7.31 | 14.0 | 40.9 | 55.9 | 19.2 | 34.3 | 864.0 | 7.0 |
| | | 5516 | 8.2 | 7.82 | 14.7 | 43.2 | 55.2 | 18.8 | 34.1 | 1073.0 | 13.6 |
| | | 5517 | 5.8 | 7.52 | 14.7 | 42.7 | 56.8 | 19.5 | 34.3 | 938.0 | 17.4 |
| | | 5518 | 14.0 | 7.65 | 14.6 | 42.4 | 55.4 | 19.1 | 34.5 | 998.0 | 73.1 |
| | | 5519 | 9.5 | 7.59 | 14.9 | 42.8 | 56.4 | 19.6 | 34.8 | 1097.0 | 10.4 |
| | | 5520 | 8.4 | 8.11 | 14.9 | 42.7 | 52.7 | 18.4 | 34.9 | 1085.0 | 13.9 |
| | | 5521 | 10.4 | 7.36 | 13.9 | 39.4 | 53.5 | 18.8 | 35.2 | 1012.0 | 6.5 |
| | | 5522 | 7.2 | 7.76 | 14.3 | 41.3 | 53.3 | 18.4 | 34.5 | 1200.0 | 13.5 |
| | | 5523 | 7.0 | 7.66 | 14.5 | 41.8 | 54.6 | 18.9 | 34.6 | 993.0 | 11.0 |
| | | Mean | 8.80 | 7.682 | 14.58 | 42.17 | 54.92 | 18.97 | 34.56 | 1015.40 | 18.14 |
| | | S.D. | 2.35 | 0.261 | 0.43 | 1.40 | 1.37 | 0.40 | 0.33 | 101.85 | 19.61 |
| | | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

| Group | Sex | Animal | Abs Neut 10^3/uL | Lymph % | Abs Lymph 10^3/uL | Mono % | Abs Mono 10^3/uL | Eosin % | Abs Eosin 10^3/uL | Baso % | Abs Baso 10^3/uL |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | m | 5514 | 1.530 | 77.0 | 7.860 | 5.6 | 0.575 | 1.3 | 0.135 | 1.0 | 0.103 |
| | | 5515 | 0.510 | 87.2 | 6.340 | 3.4 | 0.247 | 1.3 | 0.091 | 1.1 | 0.083 |
| | | 5516 | 1.120 | 74.1 | 6.110 | 8.3 | 0.680 | 2.9 | 0.239 | 1.2 | 0.098 |
| | | 5517 | 1.020 | 74.7 | 4.360 | 5.4 | 0.317 | 2.1 | 0.120 | 0.4 | 0.021 |
| | | 5518 | 10.300 | 19.1 | 2.680 | 6.2 | 0.873 | 0.8 | 0.117 | 0.7 | 0.093 |
| | | 5519 | 0.986 | 85.4 | 8.070 | 2.8 | 0.265 | 1.1 | 0.108 | 0.2 | 0.022 |
| | | 5520 | 1.170 | 82.3 | 6.920 | 2.3 | 0.189 | 1.2 | 0.099 | 0.3 | 0.028 |
| | | 5521 | 0.675 | 86.1 | 8.920 | 5.1 | 0.529 | 1.6 | 0.164 | 0.7 | 0.070 |
| | | 5522 | 0.968 | 81.2 | 5.820 | 3.2 | 0.232 | 1.5 | 0.110 | 0.5 | 0.039 |
| | | 5523 | 0.770 | 78.5 | 5.500 | 6.8 | 0.479 | 2.9 | 0.206 | 0.7 | 0.049 |
| | | Mean | 1.9049 | 74.56 | 6.2580 | 4.91 | 0.4386 | 1.67 | 0.1389 | 0.68 | 0.0606 |
| | | S.D. | 2.9632 | 20.03 | 1.8431 | 1.94 | 0.2266 | 0.73 | 0.0491 | 0.34 | 0.0326 |
| | | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix N

## Clinical Pathology

## ATTACHMENT 2(continued): Individual Hematology -Male

Day: 30 relative to Start Date

| Group | Sex | Animal | WBC 10^3/uL | RBC 10^6/uL | HGB g/dL | HCT % | MCV fL | MCH pg | MCHC g/dL | PLT 10^3/uL | Neutro % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | m | 5544 | 8.6 | 7.07 | 13.1 | 38.8 | 54.8 | 18.6 | 33.9 | 1177.0 | 25.8 |
| | | 5545 | 7.1 | 7.51 | 14.1 | 41.4 | 55.1 | 18.7 | 34.0 | 1066.0 | 11.9 |
| | | 5546 | 10.3 | 7.02 | 13.8 | 41.1 | 58.6 | 19.7 | 33.7 | 958.0 | 23.3 |
| | | 5547 | 7.1 | 7.90 | 14.5 | 42.7 | 54.0 | 18.3 | 33.9 | 776.0 | 11.3 |
| | | 5548 | 9.9 | 7.43 | 14.3 | 42.8 | 57.7 | 19.3 | 33.5 | 927.0 | 14.8 |
| | | 5549 | 10.5 | 7.16 | 14.2 | 41.7 | 58.3 | 19.9 | 34.1 | 872.0 | 10.3 |
| | | 5550 | 7.1 | 7.62 | 14.3 | 41.8 | 54.8 | 18.8 | 34.3 | 842.0 | 21.2 |
| | | 5551 | 7.6 | 7.42 | 14.1 | 41.6 | 56.1 | 19.0 | 33.9 | 944.0 | 7.8 |
| | | 5552 | 5.4 | 7.30 | 14.4 | 41.4 | 56.7 | 19.8 | 34.8 | 785.0 | 9.0 |
| | | 5553 | 5.1 | 7.19 | 14.1 | 40.2 | 55.9 | 19.6 | 35.0 | 737.0 | 11.6 |
| | | Mean | 7.87 | 7.362 | 14.09 | 41.35 | 56.20 | 19.17 | 34.11 | 908.40 | 14.72 |
| | | S.D. | 1.92 | 0.271 | 0.40 | 1.16 | 1.59 | 0.57 | 0.47 | 137.00 | 6.38 |
| | | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

| Group | Sex | Animal | Abs Neut 10^3/uL | Lymph % | Abs Lymph 10^3/uL | Mono % | Abs Mono 10^3/uL | Eosin % | Abs Eosin 10^3/uL | Baso % | Abs Baso 10^3/uL |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | m | 5544 | 2.220 | 65.5 | 5.640 | 5.4 | 0.463 | 2.0 | 0.174 | 1.3 | 0.109 |
| | | 5545 | 0.841 | 81.0 | 5.740 | 5.3 | 0.375 | 1.0 | 0.070 | 0.9 | 0.063 |
| | | 5546 | 2.400 | 64.4 | 6.650 | 8.4 | 0.863 | 3.0 | 0.312 | 0.9 | 0.093 |
| | | 5547 | 0.797 | 80.5 | 5.690 | 6.3 | 0.448 | 0.8 | 0.054 | 1.2 | 0.081 |
| | | 5548 | 1.470 | 78.5 | 7.770 | 5.1 | 0.502 | 1.1 | 0.111 | 0.6 | 0.056 |
| | | 5549 | 1.090 | 81.5 | 8.550 | 5.8 | 0.603 | 1.9 | 0.204 | 0.5 | 0.055 |
| | | 5550 | 1.510 | 72.5 | 5.160 | 4.7 | 0.335 | 1.4 | 0.097 | 0.3 | 0.020 |
| | | 5551 | 0.592 | 86.4 | 6.580 | 3.5 | 0.266 | 2.0 | 0.151 | 0.3 | 0.023 |
| | | 5552 | 0.490 | 82.4 | 4.480 | 6.2 | 0.339 | 1.5 | 0.081 | 0.8 | 0.046 |
| | | 5553 | 0.596 | 77.3 | 3.910 | 7.9 | 0.397 | 1.5 | 0.077 | 1.5 | 0.078 |
| | | Mean | 1.2006 | 77.00 | 6.0170 | 5.86 | 0.4591 | 1.62 | 0.1331 | 0.83 | 0.0624 |
| | | S.D. | 0.6824 | 7.30 | 1.4169 | 1.45 | 0.1712 | 0.64 | 0.0795 | 0.41 | 0.0287 |
| | | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix N

## Clinical Pathology

## ATTACHMENT 2 (continued): Individual Hematology -Male

Day: 30 relative to Start Date

| Group | Sex | Animal | WBC 10^3/uL | RBC 10^6/uL | HGB g/dL | HCT % | MCV fL | MCH pg | MCHC g/dL | PLT 10^3/uL | Neutro % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 4 | m | 5574 | 8.2 | 6.95 | 12.6 | 36.9 | 53.1 | 18.1 | 34.0 | 744.0 | 13.1 |
| | | 5575 | 7.1 | 7.53 | 14.3 | 42.1 | 55.9 | 19.0 | 34.0 | 992.0 | 20.2 |
| | | 5576 | 5.3 | 7.39 | 13.9 | 41.7 | 56.4 | 18.8 | 33.4 | 698.0 | 16.8 |
| | | 5577 | 7.0 | 7.36 | 13.9 | 41.1 | 55.9 | 18.9 | 33.9 | 824.0 | 8.9 |
| | | 5578 | 6.2 | 7.25 | 13.4 | 39.3 | 54.2 | 18.4 | 34.0 | 1069.0 | 17.1 |
| | | 5579 | 9.0 | 7.10 | 13.2 | 39.6 | 55.8 | 18.6 | 33.4 | 876.0 | 16.2 |
| | | 5580 | 7.6 | 6.96 | 12.2 | 36.2 | 52.0 | 17.5 | 33.7 | 1129.0 | 7.5 |
| | | 5581 | 8.1 | 7.25 | 13.3 | 38.9 | 53.7 | 18.3 | 34.1 | 1197.0 | 10.4 |
| | | 5582 | 5.7 | 7.59 | 14.1 | 40.2 | 52.9 | 18.6 | 35.1 | 931.0 | 10.9 |
| | | 5583 | 7.1 | 7.82 | 14.0 | 40.3 | 51.5 | 17.9 | 34.8 | 919.0 | 18.9 |
| | | Mean | 7.13 | 7.320 | 13.49 | 39.63 | 54.14 | 18.41 | 34.04 | 937.90 | 14.00 |
| | | S.D. | 1.16 | 0.279 | 0.68 | 1.92 | 1.78 | 0.47 | 0.54 | 161.98 | 4.43 |
| | | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

| Group | Sex | Animal | Abs Neut 10^3/uL | Lymph % | Abs Lymph 10^3/uL | Mono % | Abs Mono 10^3/uL | Eosin % | Abs Eosin 10^3/uL | Baso % | Abs Baso 10^3/uL |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 4 | m | 5574 | 1.070 | 83.7 | 6.830 | 1.5 | 0.125 | 1.2 | 0.096 | 0.5 | 0.045 |
| | | 5575 | 1.440 | 74.0 | 5.280 | 2.7 | 0.191 | 3.0 | 0.211 | 0.2 | 0.013 |
| | | 5576 | 0.893 | 75.2 | 4.000 | 6.0 | 0.320 | 1.2 | 0.066 | 0.7 | 0.039 |
| | | 5577 | 0.623 | 83.7 | 5.830 | 6.0 | 0.414 | 1.0 | 0.070 | 0.4 | 0.027 |
| | | 5578 | 1.070 | 74.0 | 4.620 | 7.2 | 0.450 | 1.4 | 0.088 | 0.3 | 0.016 |
| | | 5579 | 1.450 | 79.8 | 7.150 | 2.1 | 0.192 | 1.7 | 0.151 | 0.1 | 0.010 |
| | | 5580 | 0.565 | 85.5 | 6.460 | 5.5 | 0.411 | 1.1 | 0.081 | 0.5 | 0.038 |
| | | 5581 | 0.835 | 82.1 | 6.630 | 5.4 | 0.439 | 1.4 | 0.116 | 0.6 | 0.052 |
| | | 5582 | 0.617 | 77.6 | 4.400 | 7.9 | 0.449 | 1.6 | 0.093 | 1.9 | 0.110 |
| | | 5583 | 1.340 | 68.3 | 4.820 | 10.7 | 0.755 | 1.3 | 0.092 | 0.8 | 0.058 |
| | | Mean | 0.9903 | 78.39 | 5.6020 | 5.50 | 0.3746 | 1.49 | 0.1064 | 0.60 | 0.0408 |
| | | S.D. | 0.3395 | 5.52 | 1.1274 | 2.82 | 0.1811 | 0.57 | 0.0440 | 0.51 | 0.0294 |
| | | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix N

## Clinical Pathology

## ATTACHMENT 2(continued) : Individual Prothrombin Times -Female

Day: 29 relative to Start Date

| Group | Sex | Animal | Prothrombin Time (seconds) |
|---|---|---|---|
| 1 | f | 5474 | .* |
| | | 5475 | 13.9 |
| | | 5476 | 14.0 |
| | | 5477 | 14.4 |
| | | 5478 | 14.3 |
| | | 5479 | 13.5 |
| | | 5480 | 13.0 |
| | | 5481 | 14.2 |
| | | 5482 | 13.9 |
| | | 5483 | 14.6 |
| | | ..... | ..... |
| | | Mean | 13.98 |
| | | S.D. | 0.49 |
| | | N | 9 |

| Group | Sex | Animal | Prothrombin Time (seconds) |
|---|---|---|---|
| 2 | f | 5505 | 13.7 |
| | | 5506 | 14.3 |
| | | 5507 | 13.9 |
| | | 5508 | 13.9 |
| | | 5509 | 14.4 |
| | | 5510 | 14.0 |
| | | 5511 | 13.9 |
| | | 5512 | 13.2 |
| | | 5513 | 14.3 |
| | | ..... | ..... |
| | | Mean | 13.96 |
| | | S.D. | 0.37 |
| | | N | 9 |

* = Result to left has an associated comment or marker

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix N

## Clinical Pathology

## ATTACHMENT 2(continued) : Individual Prothrombin Times -Female

Day: 29 relative to Start Date

| Group | Sex | Animal | Prothrombin Time (seconds) |
|---|---|---|---|
| 3 | f | 5534 | 13.4 |
| | | 5535 | 13.0 |
| | | 5536 | 13.5 |
| | | 5537 | 13.9 |
| | | 5538 | .* |
| | | 5539 | 12.8 |
| | | 5540 | 13.1 |
| | | 5541 | 12.9 |
| | | 5542 | 12.8 |
| | | 5543 | 13.4 |
| | | --- | --- |
| | | Mean | 13.20 |
| | | S.D. | 0.37 |
| | | N | 9 |

| Group | Sex | Animal | Prothrombin Time (seconds) |
|---|---|---|---|
| 4 | f | 5564 | 12.7 |
| | | 5565 | 13.1 |
| | | 5566 | 13.5 |
| | | 5567 | 13.5 |
| | | 5568 | 13.6 |
| | | 5569 | 12.7 |
| | | 5570 | 13.4 |
| | | 5571 | 13.6 |
| | | 5572 | 12.4 |
| | | 5573 | 12.4 |
| | | --- | --- |
| | | Mean | 13.09 |
| | | S.D. | 0.50 |
| | | N | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix N

## Clinical Pathology

## ATTACHMENT 2 (continued): Individual Prothrombin Times -Male

Day: 30 relative to Start Date

| Group | Sex | Animal | Prothrombin Time (seconds) |
|---|---|---|---|
| 1 | m | 5484 | 13.8 |
| | | 5485 | 14.8 |
| | | 5486 | 13.7 |
| | | 5487 | 14.7 |
| | | 5488 | 13.6 |
| | | 5489 | 13.6* |
| | | 5490 | 14.7 |
| | | 5491 | 13.9 |
| | | 5492 | 14.5 |
| | | 5493 | 14.0 |
| | | --- | --- |
| | | Mean | 14.13 |
| | | S.D. | 0.49 |
| | | N | 10 |

| Group | Sex | Animal | Prothrombin Time (seconds) |
|---|---|---|---|
| 2 | m | 5514 | 14.0 |
| | | 5515 | 13.7 |
| | | 5516 | 14.7 |
| | | 5517 | 14.0 |
| | | 5518 | 13.8 |
| | | 5519 | 14.0 |
| | | 5520 | 13.9 |
| | | 5521 | 14.9 |
| | | 5522 | 13.6 |
| | | 5523 | 14.0 |
| | | --- | --- |
| | | Mean | 14.06 |
| | | S.D. | 0.42 |
| | | N | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix N

## Clinical Pathology

## ATTACHMENT 2 (continued): Individual Prothrombin Times -Male

Day: 30 relative to Start Date

| Group | Sex | Animal | Prothrombin Time (seconds) |
|---|---|---|---|
| 3 | m | 5544 | 13.7 |
| | | 5545 | 14.8 |
| | | 5546 | 14.1 |
| | | 5547 | 14.9 |
| | | 5548 | 13.7 |
| | | 5549 | 14.1 |
| | | 5550 | 14.6 |
| | | 5551 | 14.9 |
| | | 5552 | 16.1 |
| | | 5553 | 17.2 |
| | | ------ | -------- |
| | | Mean | 14.81 |
| | | S.D. | 1.10 |
| | | N | 10 |

| Group | Sex | Animal | Prothrombin Time (seconds) |
|---|---|---|---|
| 4 | m | 5574 | 15.3 |
| | | 5575 | 16.6 |
| | | 5576 | 14.7 |
| | | 5577 | 15.0 |
| | | 5578 | 14.5 |
| | | 5579 | 14.9 |
| | | 5580 | 14.7 |
| | | 5581 | 18.0 |
| | | 5582 | 17.6 |
| | | 5583 | 17.3 |
| | | ------ | -------- |
| | | Mean | 15.86 |
| | | S.D. | 1.36 |
| | | N | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix N

## Clinical Pathology

## ATTACHMENT 3: HISTORICAL CONTROL DATA

Clinical Chemistry

FEMALE (Sprague Dawley 8-12 weeks)

| Parameter (Unit) | N | Mean | SD | Range |
|---|---|---|---|---|
| ALB (g/dL) | 88 | 3.9 | 0.52 | 2.9-5.2 |
| ALP (U/L) | 88 | 76.5 | 18.8 | 36-125 |
| ALT (U/L) | 88 | 22.2 | 7.1 | 11-56 |
| AST (U/L) | 88 | 77.3 | 17.7 | 49-119 |
| TBILI (mg/dL) | 88 | 0.16 | 0.0 | 0.09-0.34 |
| CA (mg/dL) | 88 | 10.0 | 0.4 | 9.4-10.9 |
| CREAT (mg/dL) | 88 | 0.4 | 0.1 | 0.3-0.6 |
| CHOL (mg/dL) | 88 | 50.6 | 12.6 | 31-99 |
| GLUC (mg/dL) | 88 | 129.9 | 16.4 | 97-179 |
| PHOS (mg/dL) | 88 | 7.0 | 0.8 | 5.0-9.2 |
| TP (g/dL) | 88 | 6.1 | 0.4 | 5.4-7.3 |
| BUN (mg/dL) | 88 | 13.6 | 2.5 | 9-20 |
| NA (mmol/L) | 88 | 140.9 | 1.5 | 137-144 |
| K (mmol/L) | 88 | 4.2 | 0.3 | 3.6-6.3 |
| CL (mmol/L) | 88 | 103.8 | 2.2 | 98-109 |

MALE (Sprague Dawley 8-12 weeks)

| Parameter (Unit) | N | Mean | SD | Range |
|---|---|---|---|---|
| ALB (g/dL) | 89 | 3.6 | 0.3 | 2.8-4.2 |
| ALP (U/L) | 89 | 135.8 | 28.6 | 80-227 |
| ALT (U/L) | 89 | 23.8 | 4.4 | 13-36 |
| AST (U/L) | 89 | 83.8 | 18.6 | 55-129 |
| TBILI (mg/dL) | 89 | 0.14 | 0.05 | 0.07-0.31 |
| CA (mg/dL) | 89 | 9.9 | 0.4 | 9.2-11.2 |
| CREAT (mg/dL) | 89 | 0.4 | 0.1 | 0.2-0.6 |
| CHOL (mg/dL) | 89 | 42.2 | 11.0 | 21-68 |
| GLUC (mg/dL) | 89 | 131.7 | 23.1 | 97-249 |
| PHOS (mg/dL) | 89 | 7.6 | 1.0 | 6.1-13.0 |
| TP (g/dL) | 89 | 5.8 | 0.3 | 5.2-6.7 |
| BUN (mg/dL) | 89 | 12.0 | 1.8 | 9-17 |
| NA (mmol/L) | 89 | 142.0 | 1.5 | 139-146 |
| K (mmol/L) | 89 | 4.6 | 0.6 | 3.9-8.4 |
| CL (mmol/L) | 89 | 103.4 | 1.7 | 99-108 |

Unaudited reference information

Data collected 2004-2008

# Appendix N

## Clinical Pathology

## ATTACHMENT 3 (continued): HISTORICAL CONTROL DATA

Hematology

FEMALE (Sprague Dawley 8-12 weeks)

| Parameter (Unit) | N | Mean | SD | Range |
|---|---|---|---|---|
| WBC ($10^3/\mu L$) | 55 | 6.6 | 2.5 | 2.9-13.5 |
| RBC ($10^6/\mu L$) | 55 | 7.50 | 0.3 | 6.80-8.20 |
| HGB (g/dL) | 55 | 14.6 | 0.5 | 13.8-15.8 |
| HCT (%) | 55 | 42.0 | 1.7 | 38.5-46.3 |
| MCV (fL) | 55 | 56.1 | 2.2 | 52.8-64.2 |
| MCH (pg) | 55 | 19.6 | 0.7 | 17.7-21.4 |
| MCHC g/dL | 55 | 34.9 | 0.9 | 32.7-36.6 |
| PLT ($10^3/\mu L$) | 55 | 1026 | 133.6 | 768-1336 |
| Neutrophil (%) | 55 | 14.0 | 6.8 | 0-29 |
| Neutrophil ($10^3/\mu L$) | 55 | 0.9 | 0.5 | 0.0-3.5 |
| Lymphocyte (%) | 55 | 78.6 | 8.1 | 60.3-95.3 |
| Lymphocyte ($10^3/\mu L$) | 55 | 5.2 | 2.2 | 2.1-12.0 |
| Monocyte (%) | 55 | 4.3 | 3.0 | 0.2-12.0 |
| Monocyte ($10^3/\mu L$) | 55 | 0.3 | 0.2 | 0.0-1.0 |
| Eosinophil (%) | 55 | 2.1 | 0.9 | 0.7-4.4 |
| Eosinophil ($10^3/\mu L$) | 55 | 0.1 | 0.1 | 0.1-0.5 |
| Basophil (%) | 55 | 1.0 | 0.9 | 0.0-4.0 |
| Basophil ($10^3/\mu L$) | 55 | 0.1 | 0.1 | 0.0-0.3 |

MALE (Sprague Dawley 8-12 weeks)

| Parameter (Unit) | N | Mean | SD | Range |
|---|---|---|---|---|
| WBC ($10^3/\mu L$) | 59 | 7.6 | 2.04 | 4.7-15.4 |
| RBC ($10^6/\mu L$) | 59 | 7.81 | 0.41 | 7.2-8.9 |
| HGB (g/dL) | 59 | 15.0 | 0.60 | 13.6-16.1 |
| HCT (%) | 59 | 42.7 | 1.51 | 40.0-45.9 |
| MCV (fL) | 59 | 54.7 | 1.86 | 50.4-59.2 |
| MCH (pg) | 59 | 19.2 | 0.66 | 18.0-20.9 |
| MCHC (g/dL) | 59 | 35.2 | 0.62 | 33.3-36.5 |
| PLT ($10^3/\mu L$) | 59 | 929 | 97.2 | 728-1167 |
| Neutrophil (%) | 59 | 15.7 | 5.81 | 4.7-34.1 |
| Neutrophil ($10^3/\mu L$) | 59 | 1.2 | 0.48 | 0.4-2.7 |
| Lymphocyte (%) | 59 | 76.8 | 6.2 | 63.3-87.4 |
| Lymphocyte ($10^3/\mu L$) | 59 | 5.9 | 1.7 | 3.4-11.2 |
| Monocyte (%) | 59 | 4.7 | 3.1 | 0.1-10.7 |
| Monocyte ($10^3/\mu L$) | 59 | 0.4 | 0.26 | 0-1.0 |
| Eosinophil (%) | 59 | 1.9 | 0.7 | 0.7-3.6 |
| Eosinophil ($10^3/\mu L$) | 59 | 0.14 | 0.05 | 0.1-0.3 |
| Basophil (%) | 59 | 0.9 | 1.03 | 0.0-3.8 |
| Basophil ($10^3/\mu L$) | 59 | 0.8 | 0.11 | 0.0-0.6 |

Unaudited reference information

Data collected 2005-2008

## Appendix N

## Clinical Pathology

## ATTACHMENT 3(continued) : HISTORICAL CONTROL DATA

Prothrombin Time

FEMALE (Sprague Dawley 8-12 weeks

| Parameter | N | Mean | SD | Range |
|---|---|---|---|---|
| Prothrombin Time (seconds) | 56 | 14.3 | 1.4 | 10.7-17.5 |

MALE (Sprague Dawley 8-12 weeks

| Parameter (Unit) | N | Mean | SD | Range |
|---|---|---|---|---|
| Prothrombin Time (seconds) | 61 | 14.8 | 1.5 | 11.6-19.5 |

# APPENDIX O

## DOW CORNING CORPORATION
## HEALTH & ENVIRONMENTAL SCIENCES

## CONTRIBUTING SCIENTIST REPORT

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| | |
|---|---|
| **Report Title:** | Morphologic Pathology for the Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test for Dimethylsilanediol (DMSD), ZMAT 4065555, in Sprague-Dawley Rats via Oral Gavage |
| **HES Study Number:** | 10872-102 |
| **Test Article:** | Dimethylsilanediol |
| **Contributing Scientist:** | James W. Crissman, D.V.M., Ph.D.<br>Diplomate, American College of Veterinary Pathologists<br>Crissman Toxicologic Pathology, LLC<br>Midland, MI 48642 |
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| **Analysis Start Date:** | November 5, 2008 |
| **Analysis End Date:** | February 25, 2009 |

# APPENDIX O

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## APPROVAL SIGNATURES

Report Title: Morphologic Pathology for the Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test for Dimethylsilanediol (DMSD), ZMAT 4065555, in Sprague-Dawley Rats via Oral Gavage

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## OBJECTIVE

The objective of this contributing scientist report is to provide gross and histopathology data for this study.

## EXPERIMENTAL

Groups of 10 rats per sex per dose were orally administered 0, 50, 250, or 500 mg/kg/day of dimethylsilanediol in corn oil by gavage for four weeks. An additional 10 females/dosage level were used to assess reproductive effects of the test article. One animal, female #5504, which was administered 50 mg/kg/day, was removed from the toxicology group and used to replace a reproductive group female that was euthanized on study day 3. Therefore, in the data that follows, N=9 for the 50 mg/kg/day females. A standard set of protocol-defined tissues was collected, weighed, and fixed in 10% neutral buffered formalin (except testes and epididymides were fixed in Bouin's solution) for all toxicity group animals (Table 1).

## DATA ANALYSIS

Microscopic examination was performed on all tissues listed in Table 1 for control group and 500 mg/kg/day animals. For animals administered 50 or 250 mg/kg/day, microscopic examination was performed as indicated in Table 2. This report includes the results for gross and histopathology on the toxicity group animals only.

## DEVIATIONS

There were no protocol deviations for this portion of the study.

## RESULTS AND DISCUSSION

### *Gross Pathology*

Gross pathology findings are summarized in Attachment 1 titled Intergroup Comparison of Gross Pathology Observations. Individual data may be found in Attachment 5, titled Individual Gross Pathology Data.

In the liver, the finding of discoloration (+/- mottled) was observed more commonly in rats of both sexes administered ≥250 mg/kg/day. Liver enlargement was grossly more notable in females administered 500 mg/kg/day. Lung discoloration was more common in male rats administered ≥250 mg/kg/day. Other findings generally occurred singly and were probably not attributable to test article administration.

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## *Microscopic Pathology*

Microscopic pathology findings are summarized in Attachment 3, Intergroup Comparison of Histopathology Observations. The same data including the identity of the animal may be found in Attachment 4, Histopathology Observations – Animal Cross Reference. Individual animal gross and histopathologic data may be found in Attachments 5 and 6.

### Liver

There were three primary liver findings as shown in Attachment 3. There was dose-related, minimal to mild, centrilobular hepatocyte hypertrophy in animals of both sexes administered ≥250 mg/kg/day. This is a common effect of xenobiotic administration and is considered an adaptive change (Cattley and Popp, 2002).

Additionally, there was minimal to moderate brown pigment accumulation in 9/10 high-dose males which was almost always associated with bile duct hyperplasia and chronic inflammation. The pigment was birefringent under polarized light, appearing bright red with Maltese cross patterns, characteristic of protophorphyrin (Greaves, 2000; DeMatteis *et al.*, 1987). The finding was split into three components and recorded as 1) protoporphyrinosis, 2) periportal chronic inflammation, and 3) bile duct hyperplasia associated with protoporphyrinosis. The severity of the inflammatory and bile duct hyperplasia components generally closely matched the pigment accumulation. The brown pigment was not observed in control animals, at lower dose levels, or in female rats.

Finally, there was minimal to moderate periportal vacuolation, consistent with increased hepatocellular lipid. The finding was characterized by numerous clear vacuoles in the cytoplasm of affected hepatocytes, a finding often termed microvesicular lipidosis. It is generally but not universally held that this finding in and of itself is not considered adverse unless severe (Cattley and Popp, 2002). It was observed in control animals of both sexes, but was more frequent and severe in females administered 500 mg/kg/day.

### Thyroid Gland

There was minimal to mild thyroid follicular cell hypertrophy in most male rats administered ≥250 mg/kg/day. The thyroid gland was considered a target only for the male rats and examined at lower dosages only for that sex. Hypertrophy of the thyroid follicular epithelium is a common secondary response to increased thyroid hormone catabolism due to up-regulation of hepatic microsomal enzymes in response to xenobiotic administration. The rat is particularly sensitive to this effect due to the species' lack of a protective carrier protein, thyroid binding globulin. (Capen *et al.*, 2002).

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## Prostate Gland

Chronic inflammation of the prostate gland is a fairly common spontaneous finding (Bosland, et al., 1998). The incidence but not the severity was increased in treated male rats, statistically identified at the highest dose, but with no evidence of a dose-response. The two most severe (moderate) instances occurred in rats administered 0 or 50 mg/kg/day, accounting for the statistical identification of a dose effect on severity; this was a negative correlation with dosage level. This finding is not considered to be attributable to test article administration.

## Lung

There was a marginal increase in minimal to mild pulmonary histiocytosis (aggregates of foamy macrophages) in male rats administered ≥250 mg/kg/day. The finding was statistically identified for both a trend in incidence and severity; however, like the control group, there were no cases graded more severe than minimal in the high dose group, so a treatment effect on severity is considered doubtful. Pulmonary histiocytosis is a very common spontaneous finding (Renne, et al., 2003). This finding is considered to be possibly attributable to test article administration.

## Other Findings

Other findings either occurred only once or were generally typical of rats of this age, stock, and test article administration method and were considered unrelated to test article administration.

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## CONCLUSIONS

Groups of 10 rats per sex per dose were orally administered 0, 50, 250, or 500 mg/kg/day of dimethylsilanediol in corn oil by gavage for four weeks. A standard set of protocol defined tissues was examined for control and high-dose groups. Suspected target tissues were examined for low- and mid-dose groups. Affects attributable to test article administration occurred in the liver and thyroid gland. There were three primary effects of the test article observed in the liver, including centrilobular hypertrophy in both sexes, periportal hepatocellular vacuolation (microvesicular lipidosis, females only), and protoporphyrinosis (males only) which was accompanied by chronic inflammation and bile duct hyperplasia. Centrilobular hypertrophy is considered an adaptive change. Hepatic lipidosis, unless severe, is generally considered non-adverse. Hepatic protoporphyrinosis is considered an adverse effect. Follicular cell hypertrophy was observed in the thyroid gland of mid- and high-dose male rats on the study. This is considered an adaptive secondary effect and adverse for the rat, but the mechanism is generally not applicable to species with significant levels of thyroid binding globulin (Capen, et al., 2002). Based on initial examination of lung and prostate gland from control and high-dose animals, these tissues were considered possible targets; however, further examination and inclusion of animals from the mid- and low-dose groups did not support this interpretation.

## REFERENCES

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## Table 1: Tissues Weighed and Collected for Histopathology Examination

| Organs Weighed | Tissues Collected |
|---|---|
| | Macroscopic lesions |
| X | Adrenal glands |
| X | Brain (including cerebrum, cerebellum and pons) |
| | Cecum |
| | Colon |
| | Duodenum |
| X | Epididymides |
| X | Heart |
| | Ileum |
| | Jejunum |
| X | Kidneys |
| X | Liver |
| | Lungs (preserved by inflation with fixative and then immersion) |
| | Lymph nodes (mediastinal and mesenteric) |
| X | Ovaries with oviducts |
| X | Prostate |
| | Sciatic nerve |
| X | Seminal vesicles |
| | Spinal cord (cervical, thoracic and lumbar) |
| X | Spleen |
| | Sternum with bone marrow |
| | Stomach |
| X | Testes |
| X | Thymus |
| | Thyroid |
| | Trachea |
| | Urinary bladder |
| X | Uterus (horns and cervix) |

## Table 2: Target Tissue Examinations, 50 and 250 mg/kg/day Groups.

| Males | Females |
|---|---|
| liver, lungs, thyroid gland, prostate gland | liver, lungs |

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## Table 3: Summary of Microscopic Findings: Toxicology Females

| | | Control (0 mg/kg/day) | | 50 mg/kg/day | | 250 mg/kg/day | | 500 mg/kg/day | |
|---|---|---|---|---|---|---|---|---|---|
| HEART; Hyperplasia; atrium; endocardium | # Examined | 10 | | 0 | | 0 | | 10 | |
| | All Grades | 0 | | 0 | | 0 | | 1 | |
| | Mild | 0 | | 0 | | 0 | | 1 | |
| KIDNEYS; Inflammation; chronic; focal | # Examined | 10 | | 0 | | 0 | | 10 | |
| | All Grades | 3 | | 0 | | 0 | | 1 | |
| | Minimal | 3 | | 0 | | 0 | | 1 | |
| KIDNEYS; Basophilia; tubular; focal | # Examined | 10 | | 0 | | 0 | | 10 | |
| | All Grades | 3 | | 0 | | 0 | | 2 | |
| | Minimal | 3 | | 0 | | 0 | | 2 | |
| LIVER; Hypertrophy; centrilobular | # Examined | 10 | | 9 | | 10 | | 10 | |
| | All Grades | 0 | +++ | 0 | | 8 | +++ | 10 | +++ |
| | Minimal | 0 | | 0 | | 4 | | 0 | |
| | Mild | 0 | | 0 | | 4 | | 10 | |
| LIVER; Inflammation; chronic; multifocal | # Examined | 10 | | 9 | | 10 | | 10 | |
| | All Grades | 7 | | 9 | | 6 | | 4 | |
| | Minimal | 6 | | 9 | | 4 | | 4 | |
| | Mild | 1 | | 0 | | 2 | | 0 | |
| LIVER; Vacuolation; hepatocellular; periportal | # Examined | 10 | | 9 | | 10 | | 10 | |
| | All Grades | 5 | +++*** | 4 | | 7 | | 10 | ++ |
| | Minimal | 3 | | 4 | | 2 | | 0 | |
| | Mild | 2 | | 0 | | 3 | | 6 | |
| | Moderate | 0 | | 0 | | 2 | | 4 | |
| LUNGS; Hemorrhage; focal | # Examined | 10 | | 9 | | 10 | | 10 | |
| | All Grades | 0 | | 1 | | 0 | | 0 | |
| | Minimal | 0 | | 1 | | 0 | | 0 | |
| LUNGS; Hyperplasia; lymphoid tissue | # Examined | 10 | | 9 | | 10 | | 10 | |
| | All Grades | 0 | | 1 | | 1 | | 0 | |
| | Mild | 0 | | 1 | | 1 | | 0 | |
| LUNGS; Inflammation; acute; focal | # Examined | 10 | | 9 | | 10 | | 10 | |
| | All Grades | 0 | | 1 | | 0 | | 0 | |
| | Minimal | 0 | | 1 | | 0 | | 0 | |

Plus Signs indicate a significant trend by the Cochran-Armitage Test across treatment groups (in the control column) or between control and a treatment group by Fisher's Exact Test with p-values of + < 0.05, ++ < 0.02 or +++ < 0.01. Asterisks indicate a significant shift in grade across treatment groups (in the control column) with p-values of * < 0.05, ** < 0.02 or *** < 0.01.

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## Table 3 (continued): Summary of Microscopic Findings: Toxicology Females

| | | Control (0 mg/kg/day) | | 50 mg/kg/day | | 250 mg/kg/day | | 500 mg/kg/day | |
|---|---|---|---|---|---|---|---|---|---|
| LUNGS; Inflammation; chronic; focal | # Examined | 10 | | 9 | | 10 | | 10 | |
| | All Grades | 0 | | 0 | | 1 | | 0 | |
| | Minimal | 0 | | 0 | | 1 | | 0 | |
| LUNGS; Histocytosis | # Examined | 10 | | 9 | | 10 | | 10 | |
| | All Grades | 3 | | 3 | | 2 | | 5 | |
| | Minimal | 3 | | 3 | | 1 | | 5 | |
| | Mild | 0 | | 0 | | 1 | | 0 | |
| OVARIES; Cyst; corpus luteum | # Examined | 10 | | 0 | | 0 | | 10 | |
| | Present | 1 | | 0 | | 0 | | 1 | |
| THYROID GLANDS; Cyst; ultimobranchial | # Examined | 10 | | 0 | | 0 | | 10 | |
| | Present | 2 | | 0 | | 0 | | 3 | |
| THYROID GLANDS; Ectopic Thymus | # Examined | 10 | | 0 | | 0 | | 10 | |
| | Present | 1 | | 0 | | 0 | | 0 | |
| THYROID GLANDS; Hypertrophy; follicular | # Examined | 10 | | 0 | | 0 | | 10 | |
| | All Grades | 0 | | 0 | | 0 | | 1 | |
| | Minimal | 0 | | 0 | | 0 | | 1 | |
| URINARY BLADDER; Inflammation; chronic; focal | # Examined | 10 | | 0 | | 0 | | 10 | |
| | All Grades | 0 | | 0 | | 0 | | 1 | |
| | Minimal | 0 | | 0 | | 0 | | 1 | |
| UTERUS; Inflammation; acute; diffuse | # Examined | 10 | | 0 | | 0 | | 10 | |
| | All Grades | 1 | | 0 | | 0 | | 0 | |
| | Mild | 1 | | 0 | | 0 | | 0 | |

Plus Signs indicate a significant trend by the Cochran-Armitage Test across treatment groups (in the control column) or between control and a treatment group by Fisher's Exact Test with p-values of + < 0.05, ++ < 0.02 or +++ < 0.01. Asterisks indicate a significant shift in grade across treatment groups (in the control column) with p-values of * < 0.05, ** < 0.02 or *** < 0.01.

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## Table 4: Summary of Microscopic Findings: Toxicology Males

| | | Control (0 mg/kg/day) | | 50 mg/kg/day | | 250 mg/kg/day | | 500 mg/kg/day | |
|---|---|---|---|---|---|---|---|---|---|
| EPIDIDYMIDES; Immature; spermatid | # Examined | 10 | | 0 | | 0 | | 10 | |
| | All Grades | 0 | | 0 | | 0 | | 1 | |
| | Minimal | 0 | | 0 | | 0 | | 1 | |
| HEART; Inflammation; chronic; focal | # Examined | 10 | | 0 | | 0 | | 10 | |
| | All Grades | 1 | | 0 | | 0 | | 1 | |
| | Minimal | 1 | | 0 | | 0 | | 1 | |
| KIDNEYS; Hyperplasia; tubular; focal | # Examined | 10 | | 0 | | 0 | | 10 | |
| | All Grades | 0 | | 0 | | 0 | | 1 | |
| | Moderate | 0 | | 0 | | 0 | | 1 | |
| KIDNEYS; Infarction; focal | # Examined | 10 | | 0 | | 0 | | 10 | |
| | All Grades | 0 | | 0 | | 0 | | 1 | |
| | Moderate | 0 | | 0 | | 0 | | 1 | |
| KIDNEYS; Inflammation; chronic; focal | # Examined | 10 | | 0 | | 0 | | 10 | |
| | All Grades | 3 | | 0 | | 0 | | 1 | |
| | Mild | 3 | | 0 | | 0 | | 1 | |
| KIDNEYS; Basophilia; tubular; focal | # Examined | 10 | | 0 | | 0 | | 10 | |
| | All Grades | 4 | | 0 | | 0 | | 5 | |
| | Minimal | 3 | | 0 | | 0 | | 4 | |
| | Mild | 1 | | 0 | | 0 | | 1 | |
| LIVER; Hypertrophy; centrilobular | # Examined | 10 | | 10 | | 10 | | 10 | |
| | All Grades | 0 | +++ | 1 | | 8 | +++ | 8 | +++ |
| | Minimal | 0 | | 1 | | 7 | | 3 | |
| | Mild | 0 | | 0 | | 1 | | 5 | |
| LIVER; Inflammation; chronic; multifocal | # Examined | 10 | | 10 | | 10 | | 10 | |
| | All Grades | 9 | | 8 | | 8 | | 1 | |
| | Minimal | 8 | | 7 | | 8 | | 1 | |
| | Mild | 1 | | 1 | | 0 | | 0 | |
| LIVER; Inflammation; chronic; periportal | # Examined | 10 | | 10 | | 10 | | 10 | |
| | All Grades | 0 | +++ | 0 | | 0 | | 9 | +++ |
| | Minimal | 0 | | 0 | | 0 | | 4 | |
| | Mild | 0 | | 0 | | 0 | | 5 | |

Plus Signs indicate a significant trend by the Cochran-Armitage Test across treatment groups (in the control column) or between control and a treatment group by Fisher's Exact Test with p-values of + < 0.05, ++ < 0.02 or +++ < 0.01. Asterisks indicate a significant shift in grade across treatment groups (in the control column) with p-values of * < 0.05, ** < 0.02 or *** < 0.01.

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## Table 4 (continued): Summary of Microscopic Findings- Toxicology Males

| | | Control (0 mg/kg/day) | | 50 mg/kg/day | | 250 mg/kg/day | | 500 mg/kg/day | |
|---|---|---|---|---|---|---|---|---|---|
| LIVER; Hyperplasia, Bile Duct, Associated with Protoporphyrinosis | # Examined | 10 | | 10 | | 10 | | 10 | |
| | All Grades | 0 | +++ | 0 | | 0 | | 8 | +++ |
| | Minimal | 0 | | 0 | | 0 | | 3 | |
| | Mild | 0 | | 0 | | 0 | | 3 | |
| | Moderate | 0 | | 0 | | 0 | | 2 | |
| LIVER; Vacuolation; hepatocellular; centrilobular | # Examined | 10 | | 10 | | 10 | | 10 | |
| | All Grades | 0 | | 1 | | 0 | | 0 | |
| | Mild | 0 | | 1 | | 0 | | 0 | |
| LIVER; Vacuolation; hepatocellular; periportal | # Examined | 10 | | 10 | | 10 | | 10 | |
| | All Grades | 2 | | 0 | | 2 | | 3 | |
| | Minimal | 1 | | 0 | | 1 | | 0 | |
| | Mild | 1 | | 0 | | 1 | | 3 | |
| LIVER; Protoporphyrinosis | # Examined | 10 | | 10 | | 10 | | 10 | |
| | All Grades | 0 | +++ | 0 | | 0 | | 9 | +++ |
| | Minimal | 0 | | 0 | | 0 | | 5 | |
| | Mild | 0 | | 0 | | 0 | | 1 | |
| | Moderate | 0 | | 0 | | 0 | | 3 | |
| LUNGS; Hemorrhage; focal | # Examined | 10 | | 10 | | 10 | | 10 | |
| | All Grades | 2 | | 0 | | 1 | | 1 | |
| | Minimal | 2 | | 0 | | 1 | | 1 | |
| LUNGS; Hyperplasia; lymphoid tissue | # Examined | 10 | | 10 | | 10 | | 10 | |
| | All Grades | 0 | | 1 | | 1 | | 0 | |
| | Mild | 0 | | 1 | | 1 | | 0 | |
| LUNGS; Inflammation; acute; focal | # Examined | 10 | | 10 | | 10 | | 10 | |
| | All Grades | 1 | | 0 | | 0 | | 0 | |
| | Minimal | 1 | | 0 | | 0 | | 0 | |
| LUNGS; Inflammation; chronic; focal | # Examined | 10 | | 10 | | 10 | | 10 | |
| | All Grades | 1 | | 0 | | 0 | | 0 | |
| | Minimal | 1 | | 0 | | 0 | | 0 | |
| LUNGS; Inflammation; chronic; multifocal | # Examined | 10 | | 10 | | 10 | | 10 | |
| | All Grades | 1 | | 0 | | 0 | | 1 | |
| | Minimal | 1 | | 0 | | 0 | | 1 | |
| LUNGS; Histocytosis | # Examined | 10 | | 10 | | 10 | | 10 | |
| | All Grades | 4 | ++* | 4 | | 8 | | 8 | |
| | Minimal | 4 | | 4 | | 4 | | 8 | |
| | Mild | 0 | | 0 | | 4 | | 0 | |

Plus Signs indicate a significant trend by the Cochran-Armitage Test across treatment groups (in the control column) or between control and a treatment group by Fisher's Exact Test with p-values of + < 0.05, ++ < 0.02 or +++ < 0.01. Asterisks indicate a significant shift in grade across treatment groups (in the control column) with p-values of * < 0.05, ** < 0.02 or *** < 0.01

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## Table 4 (continued): Summary of Microscopic Findings- Toxicology Males

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| PROSTATE GLAND; Inflammation; chronic | # Examined | 10 | | 10 | | 10 | | 10 | |
| | All Grades | 2 | +* | 6 | | 5 | | 7 | + |
| | Minimal | 0 | | 3 | | 5 | | 1 | |
| | Mild | 1 | | 2 | | 0 | | 6 | |
| | Moderate | 1 | | 1 | | 0 | | 0 | |
| PROSTATE GLAND; Inflammation; chronic-active | # Examined | 10 | | 10 | | 10 | | 10 | |
| | All Grades | 0 | | 1 | | 0 | | 0 | |
| | Marked | 0 | | 1 | | 0 | | 0 | |
| PROSTATE GLAND; Necrosis; single cell | # Examined | 10 | | 10 | | 10 | | 10 | |
| | All Grades | 1 | | 0 | | 0 | | 1 | |
| | Minimal | 1 | | 0 | | 0 | | 1 | |
| SEMINAL VESICLES; Atrophy; unilateral | # Examined | 10 | | 0 | | 0 | | 10 | |
| | All Grades | 0 | | 0 | | 0 | | 1 | |
| | Mild | 0 | | 0 | | 0 | | 1 | |
| TESTES; Degeneration; spermatid | # Examined | 10 | | 0 | | 0 | | 10 | |
| | All Grades | 0 | | 0 | | 0 | | 1 | |
| | Minimal | 0 | | 0 | | 0 | | 1 | |
| TESTES; Cyst; seminiferous tubule | # Examined | 10 | | 0 | | 0 | | 10 | |
| | Present | 0 | | 0 | | 0 | | 1 | |
| THYROID GLANDS; Cyst; ultimobranchial | # Examined | 10 | | 10 | | 10 | | 10 | |
| | Present | 2 | | 3 | | 0 | | 1 | |
| THYROID GLANDS; Ectopic Thymus | # Examined | 10 | | 10 | | 10 | | 10 | |
| | Present | 1 | | 0 | | 0 | | 0 | |
| THYROID GLANDS; Hypertrophy; follicular | # Examined | 10 | | 10 | | 10 | | 10 | |
| | All Grades | 1 | +++* | 0 | | 8 | +++ | 9 | +++ |
| | Minimal | 1 | | 0 | | 5 | | 1 | |
| | Mild | 0 | | 0 | | 3 | | 8 | |

Plus Signs indicate a significant trend by the Cochran-Armitage Test across treatment groups (in the control column) or between control and a treatment group by Fisher's Exact Test with p-values of + < 0.05, ++ < 0.02 or +++ < 0.01. Asterisks indicate a significant shift in grade across treatment groups (in the control column) with p-values of * < 0.05, ** < 0.02 or *** < 0.01

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## Attachment 1

## Intergroup Comparison of Gross Pathology Observations

| Removal Reasons: All of those SELECTED | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| ADRENAL GLANDS; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 9 | 7 | 10 | 10 | 9 | 10 | 8 |
| Discoloration; dark | (0) | (1) | (0) | (0) | (0) | (0) | (0) | (0) |
| mild | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Discoloration; red; unilateral; single | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Enlarged | (0) | (0) | (2) | (0) | (0) | (0) | (0) | (2) |
| minimal | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 |
| BONE MARROW, STERNUM; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| BRAIN; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| EPIDIDYMIDES; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (-) | (-) | (-) | (-) |
| No Visible Lesions | 10 | 10 | 10 | 10 | - | - | - | - |
| HEART; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| INTESTINE, CECUM; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| INTESTINE, COLON; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 9 | 8 | 10 | 8 | 10 | 9 |
| Dilation | 0 | 0 | 1 | 2 | 0 | 1 | 0 | 1 |
| INTESTINE, DUODENUM; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |

# APPENDIX O

## Attachment 1 (continued)

## Intergroup Comparison of Gross Pathology Observations

| Removal Reasons: All of those SELECTED | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| INTESTINE, ILEUM; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| INTESTINE, JEJUNUM; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| KIDNEYS; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 9 | 10 | 9 | 10 | 10 |
| Discoloration; yellow; unilateral | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| LIVER; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 9 | 8 | 3 | 10 | 9 | 8 | 4 |
| Discoloration | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 |
| Discoloration; mottled | 0 | 1 | 2 | 6 | 0 | 0 | 1 | 1 |
| Enlarged | 0 | 0 | 0 | 1 | 0 | 0 | (1) | (4) |
| minimal | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 3 |
| LUNGS; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 9 | 8 | 6 | 10 | 9 | 10 | 9 |
| Discoloration; focal | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 |
| Discoloration; dark; multiple | 0 | 0 | 2 | 2 | 0 | 0 | 0 | 0 |
| Hemorrhage; red; single | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| LYMPH NODE, MEDIASTINAL; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 8 | 10 | 10 |
| LYMPH NODE, MESENTERIC; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| NERVE, SCIATIC; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |

# APPENDIX O

## Attachment 1 (continued)

## Intergroup Comparison of Gross Pathology Observations

| Removal Reasons: All of those SELECTED | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| NERVE, SCIATIC; (continued) | | | | | | | | |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| OVARIES; | | | | | | | | |
| Submitted | (-) | (-) | (-) | (-) | (10) | (9) | (10) | (10) |
| No Visible Lesions | - | - | - | - | 10 | 8 | 10 | 10 |
| Enlarged | (-) | (-) | (-) | (-) | (0) | (1) | (0) | (0) |
| minimal | - | - | - | - | 0 | 1 | 0 | 0 |
| PROSTATE GLAND; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (-) | (-) | (-) | (-) |
| No Visible Lesions | 10 | 10 | 10 | 10 | - | - | - | - |
| SEMINAL VESICLES; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (-) | (-) | (-) | (-) |
| No Visible Lesions | 10 | 9 | 10 | 8 | - | - | - | - |
| Small | (0) | (1) | (0) | 1 | (-) | (-) | (-) | (-) |
| minimal | 0 | 1 | 0 | 0 | - | - | - | - |
| Enlarged | (0) | (0) | (0) | (1) | (-) | (-) | (-) | (-) |
| minimal | 0 | 0 | 0 | 1 | - | - | - | - |
| SPINAL CORD; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| SPLEEN; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 9 | 10 | 10 | 8 | 9 | 10 |
| Discoloration; dark | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Enlarged | (0) | (0) | (1) | (0) | (0) | (0) | (1) | (0) |
| minimal | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 |
| STOMACH; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| TESTES; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (-) | (-) | (-) | (-) |

# APPENDIX O

## Attachment 1 (continued)

## Intergroup Comparison of Gross Pathology Observations

| Removal Reasons: All of those SELECTED | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| TESTES; (continued) | | | | | | | | |
| No Visible Lesions | 10 | 10 | 10 | 9 | - | - | - | - |
| Discoloration; hemorrhagic; unilateral | 0 | 0 | 0 | 1 | - | - | - | - |
| THYMUS; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 9 | 10 | 6 | 5 | 10 | 7 | 10 | 10 |
| Discoloration | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Discoloration; few | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Discoloration; dark; multiple | (0) | (0) | (0) | (1) | (0) | (0) | (0) | (0) |
| minimal | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Discoloration; red; unilateral; multifocal | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Discoloration; red; multifocal | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Discoloration; red; multiple | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Enlarged | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 |
| Small | 0 | 0 | 3 | (4) | 0 | 0 | 0 | 0 |
| minimal | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| THYROID GLANDS; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| TRACHEA; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| URINARY BLADDER; | | | | | | | | |
| Submitted | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| No Visible Lesions | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| UTERUS; | | | | | | | | |
| Submitted | (-) | (-) | (-) | (-) | (10) | (9) | (10) | (10) |
| No Visible Lesions | - | - | - | - | 10 | 9 | 10 | 10 |

# APPENDIX O

## Attachment 2

## Gross Pathology Observations – Animal Cross Reference

Removal Reason: All of those selected

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| ADRENAL GLANDS; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5574 | 5474 | 5505 | 5534 | 5564 |
| | 5485 | 5515 | 5545 | 5575 | 5475 | 5506 | 5535 | 5565 |
| | 5486 | 5516 | 5547 | 5576 | 5476 | 5507 | 5536 | 5566 |
| | 5487 | 5517 | 5548 | 5577 | 5477 | 5508 | 5537 | 5567 |
| | 5488 | 5519 | 5550 | 5578 | 5478 | 5509 | 5538 | 5569 |
| | 5489 | 5520 | 5551 | 5579 | 5479 | 5510 | 5539 | 5570 |
| | 5490 | 5521 | 5552 | 5580 | 5480 | 5511 | 5540 | 5572 |
| | 5491 | 5522 | | 5581 | 5481 | 5512 | 5541 | 5573 |
| | 5492 | 5523 | | 5582 | 5482 | 5513 | 5542 | |
| | 5493 | | | 5583 | 5483 | | 5543 | |
| Discoloration; dark; mild | | 5518 | | | | | | |
| Discoloration; red; unilateral; single | | | 5546 | | | | | |
| Enlarged; minimal | | | 5549 | | | | | 5568 |
| Enlarged | | | 5553 | | | | | 5571 |
| BONE MARROW, STERNUM; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5574 | 5474 | 5505 | 5534 | 5564 |
| | 5485 | 5515 | 5545 | 5575 | 5475 | 5506 | 5535 | 5565 |
| | 5486 | 5516 | 5546 | 5576 | 5476 | 5507 | 5536 | 5566 |
| | 5487 | 5517 | 5547 | 5577 | 5477 | 5508 | 5537 | 5567 |
| | 5488 | 5518 | 5548 | 5578 | 5478 | 5509 | 5538 | 5568 |
| | 5489 | 5519 | 5549 | 5579 | 5479 | 5510 | 5539 | 5569 |
| | 5490 | 5520 | 5550 | 5580 | 5480 | 5511 | 5540 | 5570 |
| | 5491 | 5521 | 5551 | 5581 | 5481 | 5512 | 5541 | 5571 |
| | 5492 | 5522 | 5552 | 5582 | 5482 | 5513 | 5542 | 5572 |
| | 5493 | 5523 | 5553 | 5583 | 5483 | | 5543 | 5573 |
| BRAIN; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5574 | 5474 | 5505 | 5534 | 5564 |
| | 5485 | 5515 | 5545 | 5575 | 5475 | 5506 | 5535 | 5565 |

# APPENDIX O

## Attachment 2 (continued)

## Gross Pathology Observations – Animal Cross Reference

| Removal Reason: All of those selected | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| BRAIN; (continued) | | | | | | | | |
| No Visible Lesions (continued) | 5488 | 5516 | 5546 | 5576 | 5476 | 5507 | 5536 | 5566 |
| | 5487 | 5517 | 5547 | 5577 | 5477 | 5508 | 5537 | 5567 |
| | 5488 | 5518 | 5548 | 5578 | 5478 | 5509 | 5538 | 5568 |
| | 5489 | 5519 | 5549 | 5579 | 5479 | 5510 | 5539 | 5569 |
| | 5490 | 5520 | 5550 | 5580 | 5480 | 5511 | 5540 | 5570 |
| | 5491 | 5521 | 5551 | 5581 | 5481 | 5512 | 5541 | 5571 |
| | 5492 | 5522 | 5552 | 5582 | 5482 | 5513 | 5542 | 5572 |
| | 5493 | 5523 | 5553 | 5583 | 5483 | | 5543 | 5573 |
| EPIDIDYMIDES; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (-) | (-) | (-) | (-) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5574 | | | | |
| | 5485 | 5515 | 5545 | 5575 | | | | |
| | 5486 | 5516 | 5546 | 5576 | | | | |
| | 5487 | 5517 | 5547 | 5577 | | | | |
| | 5488 | 5518 | 5548 | 5578 | | | | |
| | 5489 | 5519 | 5549 | 5579 | | | | |
| | 5490 | 5520 | 5550 | 5580 | | | | |
| | 5491 | 5521 | 5551 | 5581 | | | | |
| | 5492 | 5522 | 5552 | 5582 | | | | |
| | 5493 | 5523 | 5553 | 5583 | | | | |
| HEART; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5574 | 5474 | 5505 | 5534 | 5564 |
| | 5485 | 5515 | 5545 | 5575 | 5475 | 5506 | 5535 | 5565 |
| | 5486 | 5516 | 5546 | 5576 | 5476 | 5507 | 5536 | 5566 |
| | 5487 | 5517 | 5547 | 5577 | 5477 | 5508 | 5537 | 5567 |
| | 5488 | 5518 | 5548 | 5578 | 5478 | 5509 | 5538 | 5568 |
| | 5489 | 5519 | 5549 | 5579 | 5479 | 5510 | 5539 | 5569 |
| | 5490 | 5520 | 5550 | 5580 | 5480 | 5511 | 5540 | 5570 |
| | 5491 | 5521 | 5551 | 5581 | 5481 | 5512 | 5541 | 5571 |
| | 5492 | 5522 | 5552 | 5582 | 5482 | 5513 | 5542 | 5572 |
| | 5493 | 5523 | 5553 | 5583 | 5483 | | 5543 | 5573 |
| INTESTINE, CECUM; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5574 | 5474 | 5505 | 5534 | 5564 |
| | 5485 | 5515 | 5545 | 5575 | 5475 | 5506 | 5535 | 5565 |

# APPENDIX O

## Attachment 2 (continued)

## Gross Pathology Observations – Animal Cross Reference

Removal Reason: All of those selected

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| INTESTINE, CECUM; (continued) | | | | | | | | |
| No Visible Lesions (continued) | 5486 | 5516 | 5546 | 5576 | 5476 | 5507 | 5536 | 5566 |
| | 5487 | 5517 | 5547 | 5577 | 5477 | 5508 | 5537 | 5567 |
| | 5488 | 5518 | 5548 | 5578 | 5478 | 5509 | 5538 | 5568 |
| | 5489 | 5519 | 5549 | 5579 | 5479 | 5510 | 5539 | 5569 |
| | 5490 | 5520 | 5550 | 5580 | 5460 | 5511 | 5540 | 5570 |
| | 5491 | 5521 | 5551 | 5581 | 5481 | 5512 | 5541 | 5571 |
| | 5492 | 5522 | 5552 | 5582 | 5462 | 5513 | 5542 | 5572 |
| | 5493 | 5523 | 5553 | 5583 | 5463 | | 5543 | 5573 |
| INTESTINE, COLON; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5575 | 5474 | 5505 | 5534 | 5564 |
| | 5485 | 5515 | 5545 | 5576 | 5475 | 5506 | 5535 | 5565 |
| | 5486 | 5516 | 5546 | 5577 | 5476 | 5507 | 5536 | 5566 |
| | 5487 | 5517 | 5547 | 5578 | 5477 | 5508 | 5537 | 5567 |
| | 5488 | 5518 | 5548 | 5580 | 5478 | 5509 | 5538 | 5568 |
| | 5489 | 5519 | 5549 | 5581 | 5479 | 5510 | 5539 | 5570 |
| | 5490 | 5520 | 5550 | 5582 | 5480 | 5511 | 5540 | 5571 |
| | 5491 | 5521 | 5551 | 5583 | 5461 | 5512 | 5541 | 5572 |
| | 5492 | 5522 | 5552 | | 5482 | | 5542 | 5573 |
| | 5493 | 5523 | | | 5483 | | 5543 | |
| Dilation | | | 5553 | 5574 | | 5513 | | 5569 |
| | | | | 5579 | | | | |
| INTESTINE, DUODENUM; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5574 | 5474 | 5505 | 5534 | 5564 |
| | 5485 | 5515 | 5545 | 5575 | 5475 | 5506 | 5535 | 5565 |
| | 5486 | 5516 | 5546 | 5576 | 5476 | 5507 | 5536 | 5566 |
| | 5487 | 5517 | 5547 | 5577 | 5477 | 5508 | 5537 | 5567 |
| | 5488 | 5518 | 5548 | 5578 | 5478 | 5509 | 5538 | 5568 |
| | 5489 | 5519 | 5549 | 5579 | 5479 | 5510 | 5539 | 5569 |
| | 5490 | 5520 | 5550 | 5580 | 5480 | 5511 | 5540 | 5570 |
| | 5491 | 5521 | 5551 | 5581 | 5481 | 5512 | 5541 | 5571 |
| | 5492 | 5522 | 5552 | 5582 | 5482 | 5513 | 5542 | 5572 |
| | 5493 | 5523 | 5553 | 5583 | 5483 | | 5543 | 5573 |

# APPENDIX O

## Attachment 2 (continued)

## Gross Pathology Observations – Animal Cross Reference

Removal Reason: All of those selected

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| INTESTINE, ILEUM; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5574 | 5474 | 5505 | 5534 | 5564 |
| | 5485 | 5515 | 5545 | 5575 | 5475 | 5506 | 5535 | 5565 |
| | 5486 | 5516 | 5546 | 5576 | 5476 | 5507 | 5536 | 5566 |
| | 5487 | 5517 | 5547 | 5577 | 5477 | 5508 | 5537 | 5567 |
| | 5488 | 5518 | 5548 | 5578 | 5478 | 5509 | 5538 | 5568 |
| | 5489 | 5519 | 5549 | 5579 | 5479 | 5510 | 5539 | 5569 |
| | 5490 | 5520 | 5550 | 5580 | 5480 | 5511 | 5540 | 5570 |
| | 5491 | 5521 | 5551 | 5581 | 5481 | 5512 | 5541 | 5571 |
| | 5492 | 5522 | 5552 | 5582 | 5482 | 5513 | 5542 | 5572 |
| | 5493 | 5523 | 5553 | 5583 | 5483 | | 5543 | 5573 |
| INTESTINE, JEJUNUM; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5574 | 5474 | 5505 | 5534 | 5564 |
| | 5485 | 5515 | 5545 | 5575 | 5475 | 5506 | 5535 | 5565 |
| | 5486 | 5516 | 5546 | 5576 | 5476 | 5507 | 5536 | 5566 |
| | 5487 | 5517 | 5547 | 5577 | 5477 | 5508 | 5537 | 5567 |
| | 5488 | 5518 | 5548 | 5578 | 5478 | 5509 | 5538 | 5568 |
| | 5489 | 5519 | 5549 | 5579 | 5479 | 5510 | 5539 | 5569 |
| | 5490 | 5520 | 5550 | 5580 | 5460 | 5511 | 5540 | 5570 |
| | 5491 | 5521 | 5551 | 5581 | 5481 | 5512 | 5541 | 5571 |
| | 5492 | 5522 | 5552 | 5582 | 5482 | 5513 | 5542 | 5572 |
| | 5493 | 5523 | 5553 | 5583 | 5483 | | 5543 | 5573 |
| KIDNEYS; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5574 | 5474 | 5505 | 5534 | 5564 |
| | 5485 | 5515 | 5545 | 5575 | 5475 | 5506 | 5535 | 5565 |
| | 5486 | 5516 | 5546 | 5576 | 5476 | 5507 | 5536 | 5566 |
| | 5487 | 5517 | 5547 | 5577 | 5477 | 5508 | 5537 | 5587 |
| | 5488 | 5518 | 5548 | 5578 | 5478 | 5509 | 5538 | 5588 |
| | 5489 | 5519 | 5549 | 5579 | 5479 | 5510 | 5539 | 5569 |
| | 5490 | 5520 | 5550 | 5580 | 5480 | 5511 | 5540 | 5570 |
| | 5491 | 5521 | 5551 | 5582 | 5481 | 5512 | 5541 | 5571 |
| | 5492 | 5522 | 5552 | 5583 | 5482 | 5513 | 5542 | 5572 |
| | 5493 | 5523 | 5553 | | 5483 | | 5543 | 5573 |
| Discoloration; yellow; unilateral | | | | 5581 | | | | |

# APPENDIX O

## Attachment 2 (continued)

## Gross Pathology Observations – Animal Cross Reference

Removal Reason: All of those selected

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| LIVER; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5574 | 5474 | 5505 | 5534 | 5564 |
| | 5485 | 5515 | 5545 | 5575 | 5475 | 5506 | 5535 | 5565 |
| | 5486 | 5516 | 5547 | 5582 | 5476 | 5507 | 5536 | 5566 |
| | 5487 | 5518 | 5548 | | 5477 | 5508 | 5537 | 5567 |
| | 5488 | 5519 | 5550 | | 5478 | 5509 | 5538 | |
| | 5489 | 5520 | 5551 | | 5479 | 5510 | 5539 | |
| | 5490 | 5521 | 5552 | | 5480 | 5511 | 5540 | |
| | 5491 | 5522 | 5553 | | 5481 | 5512 | 5541 | |
| | 5492 | 5523 | | | 5482 | 5513 | | |
| | 5493 | | | | 5483 | | | |
| Discoloration | | | | | | | 5543 | 5570 |
| | | | | | | | | 5573 |
| Discoloration; mottled | | 5517 | 5546 | 5576 | | | 5542 | 5572 |
| | | | 5549 | 5577 | | | | |
| | | | | 5578 | | | | |
| | | | | 5579 | | | | |
| | | | | 5580 | | | | |
| | | | | 5581 | | | | |
| Enlarged; minimal | | | | | | | 5543 | 5568 |
| | | | | | | | | 5569 |
| | | | | | | | | 5573 |
| Enlarged | | | | 5583 | | | | 5571 |
| LUNGS; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5575 | 5474 | 5505 | 5534 | 5564 |
| | 5485 | 5515 | 5545 | 5579 | 5475 | 5506 | 5535 | 5565 |
| | 5486 | 5517 | 5548 | 5580 | 5476 | 5507 | 5536 | 5566 |
| | 5487 | 5518 | 5549 | 5581 | 5477 | 5508 | 5537 | 5568 |
| | 5488 | 5519 | 5550 | 5582 | 5478 | 5509 | 5538 | 5569 |
| | 5489 | 5520 | 5551 | 5583 | 5479 | 5510 | 5539 | 5570 |
| | 5490 | 5521 | 5552 | | 5480 | 5511 | 5540 | 5571 |
| | 5491 | 5522 | 5553 | | 5481 | 5512 | 5541 | 5572 |

# APPENDIX O

## Attachment 2 (continued)

## Gross Pathology Observations – Animal Cross Reference

Removal Reason: All of those selected

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| LUNGS; (continued) | | | | | | | | |
| No Visible Lesions (continued) | 5492<br>5493 | 5523 | | | 5482<br>5483 | 5513 | 5542<br>5543 | 5573 |
| Discoloration; dark; multiple | | | 5546<br>5547 | 5576<br>5578 | | | | |
| Discoloration; focal | | 5516 | | 5574 | | | | |
| Hemorrhage; red; single | | | | 5577 | | | | |
| LYMPH NODE, MEDIASTINAL; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484<br>5485<br>5486<br>5487<br>5488<br>5489<br>5490<br>5491<br>5492<br>5493 | 5514<br>5515<br>5516<br>5517<br>5518<br>5519<br>5520<br>5521<br>5522<br>5523 | 5544<br>5545<br>5546<br>5547<br>5548<br>5549<br>5550<br>5551<br>5552<br>5553 | 5574<br>5575<br>5576<br>5577<br>5578<br>5579<br>5580<br>5581<br>5582<br>5583 | 5474<br>5475<br>5476<br>5477<br>5478<br>5479<br>5480<br>5481<br>5482<br>5483 | 5505<br>5506<br>5507<br>5508<br>5509<br>5510<br>5511<br>5512<br>5513 | 5534<br>5535<br>5536<br>5537<br>5538<br>5539<br>5540<br>5541<br>5542<br>5543 | 5564<br>5565<br>5566<br>5567<br>5568<br>5569<br>5570<br>5571<br>5572<br>5573 |
| LYMPH NODE, MESENTERIC; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484<br>5485<br>5486<br>5487<br>5488<br>5489<br>5490<br>5491<br>5492<br>5493 | 5514<br>5515<br>5516<br>5517<br>5518<br>5519<br>5520<br>5521<br>5522<br>5523 | 5544<br>5545<br>5546<br>5547<br>5548<br>5549<br>5550<br>5551<br>5552<br>5553 | 5574<br>5575<br>5576<br>5577<br>5578<br>5579<br>5580<br>5581<br>5582<br>5583 | 5474<br>5475<br>5476<br>5477<br>5478<br>5479<br>5480<br>5481<br>5482<br>5483 | 5505<br>5506<br>5507<br>5508<br>5509<br>5510<br>5511<br>5512<br>5513 | 5534<br>5535<br>5536<br>5537<br>5538<br>5539<br>5540<br>5541<br>5542<br>5543 | 5564<br>5565<br>5566<br>5567<br>5568<br>5569<br>5570<br>5571<br>5572<br>5573 |
| NERVE, SCIATIC; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5574 | 5474 | 5505 | 5534 | 5584 |

# APPENDIX O

## Attachment 2 (continued)

## Gross Pathology Observations – Animal Cross Reference

| Removal Reason: All of those selected | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| NERVE, SCIATIC; (continued) | | | | | | | | |
| No Visible Lesions (continued) | 5485 | 5515 | 5545 | 5575 | 5475 | 5506 | 5535 | 5565 |
| | 5486 | 5516 | 5546 | 5576 | 5476 | 5507 | 5536 | 5566 |
| | 5487 | 5517 | 5547 | 5577 | 5477 | 5508 | 5537 | 5567 |
| | 5488 | 5518 | 5548 | 5578 | 5478 | 5509 | 5538 | 5568 |
| | 5489 | 5519 | 5549 | 5579 | 5479 | 5510 | 5539 | 5569 |
| | 5490 | 5520 | 5550 | 5580 | 5480 | 5511 | 5540 | 5570 |
| | 5491 | 5521 | 5551 | 5581 | 5481 | 5512 | 5541 | 5571 |
| | 5492 | 5522 | 5552 | 5582 | 5482 | 5513 | 5542 | 5572 |
| | 5493 | 5523 | 5553 | 5583 | 5483 | | 5543 | 5573 |
| OVARIES; | | | | | | | | |
| Submitted | (-) | (-) | (-) | (-) | (10) | (9) | (10) | (10) |
| No Visible Lesions | | | | | 5474 | 5505 | 5534 | 5564 |
| | | | | | 5475 | 5506 | 5535 | 5565 |
| | | | | | 5476 | 5507 | 5536 | 5566 |
| | | | | | 5477 | 5508 | 5537 | 5567 |
| | | | | | 5478 | 5509 | 5538 | 5568 |
| | | | | | 5479 | 5510 | 5539 | 5569 |
| | | | | | 5480 | 5511 | 5540 | 5570 |
| | | | | | 5481 | 5512 | 5541 | 5571 |
| | | | | | 5482 | | 5542 | 5572 |
| | | | | | 5483 | | 5543 | 5573 |
| Enlarged; | | | | | | | | |
| minimal | | | | | | 5513 | | |
| PROSTATE GLAND; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (-) | (-) | (-) | (-) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5574 | | | | |
| | 5485 | 5515 | 5545 | 5575 | | | | |
| | 5486 | 5516 | 5546 | 5576 | | | | |
| | 5487 | 5517 | 5547 | 5577 | | | | |
| | 5488 | 5518 | 5548 | 5578 | | | | |
| | 5489 | 5519 | 5549 | 5579 | | | | |
| | 5490 | 5520 | 5550 | 5580 | | | | |
| | 5491 | 5521 | 5551 | 5581 | | | | |
| | 5492 | 5522 | 5552 | 5582 | | | | |
| | 5493 | 5523 | 5553 | 5583 | | | | |

# APPENDIX O

## Attachment 2 (continued)

## Gross Pathology Observations – Animal Cross Reference

Removal Reason: All of those selected

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| SEMINAL VESICLES; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (-) | (-) | (-) | (-) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5574 | | | | |
| | 5485 | 5515 | 5545 | 5575 | | | | |
| | 5486 | 5516 | 5546 | 5577 | | | | |
| | 5487 | 5517 | 5547 | 5578 | | | | |
| | 5488 | 5518 | 5548 | 5579 | | | | |
| | 5489 | 5519 | 5549 | 5580 | | | | |
| | 5490 | 5520 | 5550 | 5581 | | | | |
| | 5491 | 5521 | 5551 | 5582 | | | | |
| | 5492 | 5522 | 5552 | | | | | |
| | 5493 | | 5553 | | | | | |
| Small; minimal | | 5523 | | | | | | |
| Small | | | | 5576 | | | | |
| Enlarged; minimal | | | | 5583 | | | | |
| SPINAL CORD; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5574 | 5474 | 5505 | 5534 | 5564 |
| | 5485 | 5515 | 5545 | 5575 | 5475 | 5506 | 5535 | 5565 |
| | 5486 | 5516 | 5546 | 5576 | 5476 | 5507 | 5536 | 5566 |
| | 5487 | 5517 | 5547 | 5577 | 5477 | 5508 | 5537 | 5567 |
| | 5488 | 5518 | 5548 | 5578 | 5478 | 5509 | 5538 | 5568 |
| | 5489 | 5519 | 5549 | 5579 | 5479 | 5510 | 5539 | 5569 |
| | 5490 | 5520 | 5550 | 5580 | 5480 | 5511 | 5540 | 5570 |
| | 5491 | 5521 | 5551 | 5581 | 5481 | 5512 | 5541 | 5571 |
| | 5492 | 5522 | 5552 | 5582 | 5482 | 5513 | 5542 | 5572 |
| | 5493 | 5523 | 5553 | 5583 | 5483 | | 5543 | 5573 |
| SPLEEN; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5574 | 5474 | 5505 | 5534 | 5564 |
| | 5485 | 5515 | 5545 | 5575 | 5475 | 5506 | 5535 | 5565 |
| | 5486 | 5516 | 5546 | 5576 | 5476 | 5507 | 5536 | 5566 |
| | 5487 | 5517 | 5547 | 5577 | 5477 | 5508 | 5537 | 5567 |

# APPENDIX O

## Attachment 2 (continued)

## Gross Pathology Observations – Animal Cross Reference

Removal Reason: All of those selected

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| SPLEEN; (continued) | | | | | | | | |
| No Visible Lesions (continued) | 5488 | 5518 | 5548 | 5578 | 5478 | 5509 | 5538 | 5568 |
| | 5489 | 5519 | 5549 | 5579 | 5479 | 5511 | 5539 | 5569 |
| | 5490 | 5520 | 5551 | 5580 | 5480 | 5512 | 5540 | 5570 |
| | 5491 | 5521 | 5552 | 5581 | 5481 | 5513 | 5541 | 5571 |
| | 5492 | 5522 | 5553 | 5582 | 5482 | | 5543 | 5572 |
| | 5493 | 5523 | | 5583 | 5483 | | | 5573 |
| Discoloration; dark | | | | | | 5510 | | |
| Enlarged; minimal | | | 5550 | | | | 5542 | |
| STOMACH; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5574 | 5474 | 5505 | 5534 | 5564 |
| | 5485 | 5515 | 5545 | 5575 | 5475 | 5508 | 5535 | 5565 |
| | 5488 | 5516 | 5546 | 5576 | 5476 | 5507 | 5536 | 5566 |
| | 5487 | 5517 | 5547 | 5577 | 5477 | 5508 | 5537 | 5567 |
| | 5488 | 5518 | 5548 | 5578 | 5478 | 5509 | 5538 | 5568 |
| | 5489 | 5519 | 5549 | 5579 | 5479 | 5510 | 5539 | 5569 |
| | 5490 | 5520 | 5550 | 5580 | 5480 | 5511 | 5540 | 5570 |
| | 5491 | 5521 | 5551 | 5581 | 5481 | 5512 | 5541 | 5571 |
| | 5492 | 5522 | 5552 | 5582 | 5482 | 5513 | 5542 | 5572 |
| | 5493 | 5523 | 5553 | 5583 | 5483 | | 5543 | 5573 |
| TESTES; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (-) | (-) | (-) | (-) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5574 | | | | |
| | 5485 | 5515 | 5545 | 5575 | | | | |
| | 5486 | 5516 | 5546 | 5576 | | | | |
| | 5487 | 5517 | 5547 | 5577 | | | | |
| | 5488 | 5518 | 5548 | 5578 | | | | |
| | 5489 | 5519 | 5549 | 5579 | | | | |
| | 5490 | 5520 | 5550 | 5580 | | | | |
| | 5491 | 5521 | 5551 | 5582 | | | | |
| | 5492 | 5522 | 5552 | 5583 | | | | |
| | 5493 | 5523 | 5553 | | | | | |
| Discoloration; hemorrhagic; unilateral | | | | 5581 | | | | |

# APPENDIX O

## Attachment 2 (continued)

## Gross Pathology Observations – Animal Cross Reference

Removal Reason: All of those selected

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| THYMUS; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5485<br>5486<br>5487<br>5488<br>5489<br>5490<br>5491<br>5492<br>5493 | 5514<br>5515<br>5516<br>5517<br>5518<br>5519<br>5520<br>5521<br>5522<br>5523 | 5544<br>5545<br>5546<br>5549<br>5550<br>5551 | 5574<br>5575<br>5577<br>5579<br>5582 | 5474<br>5475<br>5476<br>5477<br>5478<br>5479<br>5480<br>5481<br>5482<br>5483 | 5505<br>5507<br>5508<br>5509<br>5510<br>5511<br>5512 | 5534<br>5535<br>5536<br>5537<br>5538<br>5539<br>5540<br>5541<br>5542<br>5543 | 5564<br>5565<br>5566<br>5567<br>5568<br>5569<br>5570<br>5571<br>5572<br>5573 |
| Discoloration | | | | | | 5506 | | |
| Discoloration; dark; multiple; minimal | | | | 5581 | | | | |
| Discoloration; red; unilateral; multifocal | 5484 | | | | | | | |
| Discoloration; red; multifocal | | | | | | 5513 | | |
| Discoloration; red; multiple | | | 5547 | | | | | |
| Discoloration; few | | | 5552 | | | | | |
| Enlarged | | | | | | 5513 | | |
| Small; minimal | | | | 5578 | | | | |
| Small | | | 5547<br>5548<br>5553 | 5576<br>5580<br>5583 | | | | |
| THYROID GLANDS; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484<br>5485<br>5486 | 5514<br>5515<br>5516 | 5544<br>5545<br>5546 | 5574<br>5575<br>5576 | 5474<br>5475<br>5476 | 5505<br>5506<br>5507 | 5534<br>5535<br>5536 | 5564<br>5565<br>5568 |

# APPENDIX O

## Attachment 2 (continued)

## Gross Pathology Observations – Animal Cross Reference

Removal Reason: All of those selected

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| THYROID GLANDS; (continued) | | | | | | | | |
| No Visible Lesions (continued) | 5487 | 5517 | 5547 | 5577 | 5477 | 5508 | 5537 | 5567 |
| | 5488 | 5518 | 5548 | 5578 | 5478 | 5509 | 5538 | 5568 |
| | 5489 | 5519 | 5549 | 5579 | 5479 | 5510 | 5539 | 5569 |
| | 5490 | 5520 | 5550 | 5580 | 5480 | 5511 | 5540 | 5570 |
| | 5491 | 5521 | 5551 | 5581 | 5481 | 5512 | 5541 | 5571 |
| | 5492 | 5522 | 5552 | 5582 | 5482 | 5513 | 5542 | 5572 |
| | 5493 | 5523 | 5553 | 5583 | 5483 | | 5543 | 5573 |
| TRACHEA; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5574 | 5474 | 5505 | 5534 | 5564 |
| | 5485 | 5515 | 5545 | 5575 | 5475 | 5506 | 5535 | 5565 |
| | 5486 | 5516 | 5546 | 5576 | 5476 | 5507 | 5536 | 5566 |
| | 5487 | 5517 | 5547 | 5577 | 5477 | 5508 | 5537 | 5567 |
| | 5488 | 5518 | 5548 | 5578 | 5478 | 5509 | 5538 | 5568 |
| | 5489 | 5519 | 5549 | 5579 | 5479 | 5510 | 5539 | 5569 |
| | 5490 | 5520 | 5550 | 5580 | 5480 | 5511 | 5540 | 5570 |
| | 5491 | 5521 | 5551 | 5581 | 5481 | 5512 | 5541 | 5571 |
| | 5492 | 5522 | 5552 | 5582 | 5482 | 5513 | 5542 | 5572 |
| | 5493 | 5523 | 5553 | 5583 | 5483 | | 5543 | 5573 |
| URINARY BLADDER; | | | | | | | | |
| Submitted | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| No Visible Lesions | 5484 | | | 5574 | 5474 | | | 5564 |
| | 5485 | | | 5575 | 5475 | | | 5565 |
| | 5486 | | | 5576 | 5476 | | | 5566 |
| | 5487 | | | 5577 | 5477 | | | 5567 |
| | 5488 | | | 5578 | 5478 | | | 5568 |
| | 5489 | | | 5579 | 5479 | | | 5569 |
| | 5490 | | | 5580 | 5480 | | | 5570 |
| | 5491 | | | 5581 | 5481 | | | 5571 |
| | 5492 | | | 5582 | 5482 | | | 5572 |
| | 5493 | | | 5583 | 5483 | | | 5573 |
| UTERUS; | | | | | | | | |
| Submitted | (-) | (-) | (-) | (-) | (10) | (9) | (10) | (10) |
| No Visible Lesions | | | | | 5474 | 5505 | 5534 | 5564 |
| | | | | | 5475 | 5506 | 5535 | 5565 |
| | | | | | 5476 | 5507 | 5536 | 5566 |

# APPENDIX O

## Attachment 2 (continued)

## Gross Pathology Observations – Animal Cross Reference

Removal Reason: All of those selected

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| ADRENAL GLANDS; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5574 | 5474 | 5505 | 5534 | 5564 |
| | 5485 | 5515 | 5545 | 5575 | 5475 | 5506 | 5535 | 5565 |
| | 5486 | 5516 | 5547 | 5576 | 5476 | 5507 | 5538 | 5566 |
| | 5487 | 5517 | 5548 | 5577 | 5477 | 5508 | 5537 | 5567 |
| | 5488 | 5519 | 5550 | 5578 | 5478 | 5509 | 5538 | 5569 |
| | 5489 | 5520 | 5551 | 5579 | 5479 | 5510 | 5539 | 5570 |
| | 5490 | 5521 | 5552 | 5580 | 5480 | 5511 | 5540 | 5572 |
| | 5491 | 5522 | | 5581 | 5481 | 5512 | 5541 | 5573 |
| | 5492 | 5523 | | 5582 | 5482 | 5513 | 5542 | |
| | 5493 | | | 5583 | 5483 | | 5543 | |
| Discoloration; dark; mild | | 5518 | | | | | | |
| Discoloration; red; unilateral; single | | | 5546 | | | | | |
| Enlarged; minimal | | | 5549 | | | | | 5568 |
| Enlarged | | | 5553 | | | | | 5571 |
| BONE MARROW, STERNUM; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5574 | 5474 | 5505 | 5534 | 5564 |
| | 5485 | 5515 | 5545 | 5575 | 5475 | 5506 | 5535 | 5565 |
| | 5486 | 5516 | 5548 | 5576 | 5476 | 5507 | 5536 | 5566 |
| | 5487 | 5517 | 5547 | 5577 | 5477 | 5508 | 5537 | 5567 |
| | 5488 | 5518 | 5548 | 5578 | 5478 | 5509 | 5538 | 5568 |
| | 5489 | 5519 | 5549 | 5579 | 5479 | 5510 | 5539 | 5569 |
| | 5490 | 5520 | 5550 | 5580 | 5480 | 5511 | 5540 | 5570 |
| | 5491 | 5521 | 5551 | 5581 | 5481 | 5512 | 5541 | 5571 |
| | 5492 | 5522 | 5552 | 5582 | 5482 | 5513 | 5542 | 5572 |
| | 5493 | 5523 | 5553 | 5583 | 5483 | | 5543 | 5573 |
| BRAIN; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5574 | 5474 | 5505 | 5534 | 5564 |
| | 5485 | 5515 | 5545 | 5575 | 5475 | 5508 | 5535 | 5565 |

# APPENDIX O

## Attachment 2 (continued)

## Gross Pathology Observations – Animal Cross Reference

Removal Reason: All of those selected

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| BRAIN; (continued) | | | | | | | | |
| No Visible Lesions (continued) | 5486 | 5516 | 5546 | 5576 | 5476 | 5507 | 5536 | 5566 |
| | 5487 | 5517 | 5547 | 5577 | 5477 | 5508 | 5537 | 5567 |
| | 5488 | 5518 | 5548 | 5578 | 5478 | 5509 | 5538 | 5568 |
| | 5489 | 5519 | 5549 | 5579 | 5479 | 5510 | 5539 | 5569 |
| | 5490 | 5520 | 5550 | 5580 | 5480 | 5511 | 5540 | 5570 |
| | 5491 | 5521 | 5551 | 5581 | 5481 | 5512 | 5541 | 5571 |
| | 5492 | 5522 | 5552 | 5582 | 5482 | 5513 | 5542 | 5572 |
| | 5493 | 5523 | 5553 | 5583 | 5483 | | 5543 | 5573 |
| EPIDIDYMIDES; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (-) | (-) | (-) | (-) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5574 | | | | |
| | 5485 | 5515 | 5545 | 5575 | | | | |
| | 5486 | 5516 | 5546 | 5576 | | | | |
| | 5487 | 5517 | 5547 | 5577 | | | | |
| | 5488 | 5518 | 5548 | 5578 | | | | |
| | 5489 | 5519 | 5549 | 5579 | | | | |
| | 5490 | 5520 | 5550 | 5580 | | | | |
| | 5491 | 5521 | 5551 | 5581 | | | | |
| | 5492 | 5522 | 5552 | 5582 | | | | |
| | 5493 | 5523 | 5553 | 5583 | | | | |
| HEART; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5574 | 5474 | 5505 | 5534 | 5564 |
| | 5485 | 5515 | 5545 | 5575 | 5475 | 5506 | 5535 | 5565 |
| | 5486 | 5516 | 5546 | 5576 | 5476 | 5507 | 5538 | 5588 |
| | 5487 | 5517 | 5547 | 5577 | 5477 | 5508 | 5537 | 5587 |
| | 5488 | 5518 | 5548 | 5578 | 5478 | 5509 | 5536 | 5568 |
| | 5489 | 5519 | 5549 | 5579 | 5479 | 5510 | 5539 | 5589 |
| | 5490 | 5520 | 5550 | 5580 | 5480 | 5511 | 5540 | 5570 |
| | 5491 | 5521 | 5551 | 5581 | 5481 | 5512 | 5541 | 5571 |
| | 5492 | 5522 | 5552 | 5562 | 5482 | 5513 | 5542 | 5572 |
| | 5493 | 5523 | 5553 | 5583 | 5483 | | 5543 | 5573 |
| INTESTINE, CECUM; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5574 | 5474 | 5505 | 5534 | 5564 |
| | 5485 | 5515 | 5545 | 5575 | 5475 | 5506 | 5535 | 5565 |

# APPENDIX O

## Attachment 2 (continued)

## Gross Pathology Observations – Animal Cross Reference

Removal Reason: All of those selected

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| INTESTINE, CECUM; (continued) | | | | | | | | |
| No Visible Lesions (continued) | 5486 | 5516 | 5546 | 5576 | 5476 | 5507 | 5536 | 5566 |
| | 5487 | 5517 | 5547 | 5577 | 5477 | 5508 | 5537 | 5567 |
| | 5488 | 5518 | 5548 | 5578 | 5478 | 5509 | 5538 | 5568 |
| | 5489 | 5519 | 5549 | 5579 | 5479 | 5510 | 5539 | 5569 |
| | 5490 | 5520 | 5550 | 5580 | 5480 | 5511 | 5540 | 5570 |
| | 5491 | 5521 | 5551 | 5581 | 5481 | 5512 | 5541 | 5571 |
| | 5492 | 5522 | 5552 | 5582 | 5482 | 5513 | 5542 | 5572 |
| | 5493 | 5523 | 5553 | 5583 | 5483 | | 5543 | 5573 |
| INTESTINE, COLON; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5575 | 5474 | 5505 | 5534 | 5564 |
| | 5485 | 5515 | 5545 | 5576 | 5475 | 5506 | 5535 | 5565 |
| | 5486 | 5516 | 5546 | 5577 | 5476 | 5507 | 5536 | 5566 |
| | 5487 | 5517 | 5547 | 5578 | 5477 | 5508 | 5537 | 5567 |
| | 5488 | 5518 | 5548 | 5580 | 5478 | 5509 | 5538 | 5568 |
| | 5489 | 5519 | 5549 | 5581 | 5479 | 5510 | 5539 | 5570 |
| | 5490 | 5520 | 5550 | 5582 | 5480 | 5511 | 5540 | 5571 |
| | 5491 | 5521 | 5551 | 5583 | 5481 | 5512 | 5541 | 5572 |
| | 5492 | 5522 | 5552 | | 5482 | | 5542 | 5573 |
| | 5493 | 5523 | | | 5483 | | 5543 | |
| Dilation | | | 5553 | 5574 | | 5513 | | 5569 |
| | | | | 5579 | | | | |
| INTESTINE, DUODENUM; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5574 | 5474 | 5505 | 5534 | 5564 |
| | 5485 | 5515 | 5545 | 5575 | 5475 | 5506 | 5535 | 5565 |
| | 5486 | 5516 | 5546 | 5576 | 5476 | 5507 | 5536 | 5566 |
| | 5487 | 5517 | 5547 | 5577 | 5477 | 5508 | 5537 | 5567 |
| | 5488 | 5518 | 5548 | 5578 | 5478 | 5509 | 5538 | 5568 |
| | 5489 | 5519 | 5549 | 5579 | 5479 | 5510 | 5539 | 5569 |
| | 5490 | 5520 | 5550 | 5580 | 5480 | 5511 | 5540 | 5570 |
| | 5491 | 5521 | 5551 | 5581 | 5481 | 5512 | 5541 | 5571 |
| | 5492 | 5522 | 5552 | 5582 | 5482 | 5513 | 5542 | 5572 |
| | 5493 | 5523 | 5553 | 5583 | 5483 | | 5543 | 5573 |

# APPENDIX O

## Attachment 2 (continued)

## Gross Pathology Observations – Animal Cross Reference

| Removal Reason: All of those selected | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| INTESTINE, ILEUM; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5574 | 5474 | 5505 | 5534 | 5564 |
| | 5485 | 5515 | 5545 | 5575 | 5475 | 5506 | 5535 | 5565 |
| | 5486 | 5516 | 5546 | 5576 | 5476 | 5507 | 5536 | 5566 |
| | 5487 | 5517 | 5547 | 5577 | 5477 | 5508 | 5537 | 5567 |
| | 5488 | 5518 | 5548 | 5578 | 5478 | 5509 | 5538 | 5568 |
| | 5489 | 5519 | 5549 | 5579 | 5479 | 5510 | 5539 | 5569 |
| | 5490 | 5520 | 5550 | 5580 | 5480 | 5511 | 5540 | 5570 |
| | 5491 | 5521 | 5551 | 5581 | 5481 | 5512 | 5541 | 5571 |
| | 5492 | 5522 | 5552 | 5582 | 5482 | 5513 | 5542 | 5572 |
| | 5493 | 5523 | 5553 | 5583 | 5483 | | 5543 | 5573 |
| INTESTINE, JEJUNUM; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5574 | 5474 | 5505 | 5534 | 5564 |
| | 5485 | 5515 | 5545 | 5575 | 5475 | 5506 | 5535 | 5565 |
| | 5486 | 5516 | 5546 | 5576 | 5476 | 5507 | 5536 | 5566 |
| | 5487 | 5517 | 5547 | 5577 | 5477 | 5508 | 5537 | 5567 |
| | 5488 | 5518 | 5548 | 5578 | 5478 | 5509 | 5538 | 5568 |
| | 5489 | 5519 | 5549 | 5579 | 5479 | 5510 | 5539 | 5569 |
| | 5490 | 5520 | 5550 | 5580 | 5480 | 5511 | 5540 | 5570 |
| | 5491 | 5521 | 5551 | 5581 | 5481 | 5512 | 5541 | 5571 |
| | 5492 | 5522 | 5552 | 5582 | 5482 | 5513 | 5542 | 5572 |
| | 5493 | 5523 | 5553 | 5583 | 5483 | | 5543 | 5573 |
| KIDNEYS; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5574 | 5474 | 5505 | 5534 | 5564 |
| | 5485 | 5515 | 5545 | 5575 | 5475 | 5506 | 5535 | 5565 |
| | 5486 | 5516 | 5546 | 5576 | 5476 | 5507 | 5536 | 5566 |
| | 5487 | 5517 | 5547 | 5577 | 5477 | 5508 | 5537 | 5567 |
| | 5488 | 5518 | 5548 | 5578 | 5478 | 5509 | 5538 | 5568 |
| | 5489 | 5519 | 5549 | 5579 | 5479 | 5510 | 5539 | 5569 |
| | 5490 | 5520 | 5550 | 5580 | 5480 | 5511 | 5540 | 5570 |
| | 5491 | 5521 | 5551 | 5582 | 5481 | 5512 | 5541 | 5571 |
| | 5492 | 5522 | 5552 | 5583 | 5482 | 5513 | 5542 | 5572 |
| | 5493 | 5523 | 5553 | | 5483 | | 5543 | 5573 |
| Discoloration; yellow; unilateral | | | | 5581 | | | | |

# APPENDIX O

## Attachment 2 (continued)

## Gross Pathology Observations – Animal Cross Reference

Removal Reason: All of those selected

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| LIVER; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5574 | 5474 | 5505 | 5534 | 5564 |
| | 5485 | 5515 | 5545 | 5575 | 5475 | 5506 | 5535 | 5565 |
| | 5486 | 5516 | 5547 | 5582 | 5476 | 5507 | 5536 | 5566 |
| | 5487 | 5518 | 5548 | | 5477 | 5508 | 5537 | 5567 |
| | 5488 | 5519 | 5550 | | 5478 | 5509 | 5538 | |
| | 5489 | 5520 | 5551 | | 5479 | 5510 | 5539 | |
| | 5490 | 5521 | 5552 | | 5480 | 5511 | 5540 | |
| | 5491 | 5522 | 5553 | | 5481 | 5512 | 5541 | |
| | 5492 | 5523 | | | 5482 | 5513 | | |
| | 5493 | | | | 5483 | | | |
| Discoloration | | | | | | | 5543 | 5570 |
| | | | | | | | | 5573 |
| Discoloration; mottled | | 5517 | 5546 | 5576 | | | 5542 | 5572 |
| | | | 5549 | 5577 | | | | |
| | | | | 5578 | | | | |
| | | | | 5579 | | | | |
| | | | | 5580 | | | | |
| | | | | 5581 | | | | |
| Enlarged; minimal | | | | | | | 5543 | 5568 |
| | | | | | | | | 5569 |
| | | | | | | | | 5573 |
| Enlarged | | | | 5583 | | | | 5571 |
| LUNGS; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5575 | 5474 | 5505 | 5534 | 5564 |
| | 5485 | 5515 | 5545 | 5579 | 5475 | 5506 | 5535 | 5565 |
| | 5486 | 5517 | 5548 | 5580 | 5476 | 5507 | 5536 | 5566 |
| | 5487 | 5518 | 5549 | 5581 | 5477 | 5508 | 5537 | 5568 |
| | 5488 | 5519 | 5550 | 5582 | 5478 | 5509 | 5538 | 5569 |
| | 5489 | 5520 | 5551 | 5583 | 5479 | 5510 | 5539 | 5570 |
| | 5490 | 5521 | 5552 | | 5480 | 5511 | 5540 | 5571 |
| | 5491 | 5522 | 5553 | | 5481 | 5512 | 5541 | 5572 |

# APPENDIX O

## Attachment 2 (continued)

## Gross Pathology Observations – Animal Cross Reference

| Removal Reason: All of those selected | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| LUNGS; (continued) | | | | | | | | |
| No Visible Lesions (continued) | 5492<br>5493 | 5523 | | | 5482<br>5483 | 5513 | 5542<br>5543 | 5573 |
| Discoloration; dark; multiple | | | 5546<br>5547 | 5578<br>5578 | | | | |
| Discoloration; focal | | 5516 | | 5574 | | | | |
| Hemorrhage; red; single | | | | 5577 | | | | |
| LYMPH NODE, MEDIASTINAL; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484<br>5485<br>5486<br>5487<br>5488<br>5489<br>5490<br>5491<br>5492<br>5493 | 5514<br>5515<br>5516<br>5517<br>5518<br>5519<br>5520<br>5521<br>5522<br>5523 | 5544<br>5545<br>5546<br>5547<br>5548<br>5549<br>5550<br>5551<br>5552<br>5553 | 5574<br>5575<br>5576<br>5577<br>5578<br>5579<br>5580<br>5581<br>5582<br>5583 | 5474<br>5475<br>5476<br>5477<br>5478<br>5479<br>5480<br>5481<br>5482<br>5483 | 5505<br>5506<br>5507<br>5508<br>5509<br>5510<br>5511<br>5512<br>5513 | 5534<br>5535<br>5536<br>5537<br>5538<br>5539<br>5540<br>5541<br>5542<br>5543 | 5564<br>5565<br>5568<br>5567<br>5568<br>5569<br>5570<br>5571<br>5572<br>5573 |
| LYMPH NODE, MESENTERIC; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484<br>5485<br>5486<br>5487<br>5488<br>5489<br>5490<br>5491<br>5492<br>5493 | 5514<br>5515<br>5516<br>5517<br>5518<br>5519<br>5520<br>5521<br>5522<br>5523 | 5544<br>5545<br>5546<br>5547<br>5546<br>5549<br>5550<br>5551<br>5552<br>5553 | 5574<br>5575<br>5576<br>5577<br>5576<br>5579<br>5580<br>5581<br>5582<br>5583 | 5474<br>5475<br>5476<br>5477<br>5478<br>5479<br>5480<br>5481<br>5482<br>5483 | 5505<br>5506<br>5507<br>5508<br>5509<br>5510<br>5511<br>5512<br>5513 | 5534<br>5535<br>5538<br>5537<br>5538<br>5539<br>5540<br>5541<br>5542<br>5543 | 5564<br>5565<br>5566<br>5567<br>5568<br>5569<br>5570<br>5571<br>5572<br>5573 |
| NERVE, SCIATIC; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5574 | 5474 | 5505 | 5534 | 5564 |

# APPENDIX O

## Attachment 2 (continued)

## Gross Pathology Observations – Animal Cross Reference

Removal Reason: All of those selected

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| NERVE, SCIATIC; (continued) | | | | | | | | |
| No Visible Lesions (continued) | 5485 | 5515 | 5545 | 5575 | 5475 | 5506 | 5535 | 5565 |
| | 5486 | 5516 | 5546 | 5576 | 5476 | 5507 | 5536 | 5566 |
| | 5487 | 5517 | 5547 | 5577 | 5477 | 5508 | 5537 | 5567 |
| | 5488 | 5518 | 5548 | 5578 | 5478 | 5509 | 5538 | 5568 |
| | 5489 | 5519 | 5549 | 5579 | 5479 | 5510 | 5539 | 5569 |
| | 5490 | 5520 | 5550 | 5580 | 5480 | 5511 | 5540 | 5570 |
| | 5491 | 5521 | 5551 | 5581 | 5481 | 5512 | 5541 | 5571 |
| | 5492 | 5522 | 5552 | 5582 | 5482 | 5513 | 5542 | 5572 |
| | 5493 | 5523 | 5553 | 5583 | 5483 | | 5543 | 5573 |
| OVARIES; | | | | | | | | |
| Submitted | (-) | (-) | (-) | (-) | (10) | (9) | (10) | (10) |
| No Visible Lesions | | | | | 5474 | 5505 | 5534 | 5564 |
| | | | | | 5475 | 5506 | 5535 | 5565 |
| | | | | | 5476 | 5507 | 5536 | 5566 |
| | | | | | 5477 | 5508 | 5537 | 5567 |
| | | | | | 5478 | 5509 | 5538 | 5568 |
| | | | | | 5479 | 5510 | 5539 | 5569 |
| | | | | | 5480 | 5511 | 5540 | 5570 |
| | | | | | 5481 | 5512 | 5541 | 5571 |
| | | | | | 5482 | | 5542 | 5572 |
| | | | | | 5483 | | 5543 | 5573 |
| Enlarged; | | | | | | | | |
| minimal | | | | | | 5513 | | |
| PROSTATE GLAND; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (-) | (-) | (-) | (-) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5574 | | | | |
| | 5485 | 5515 | 5545 | 5575 | | | | |
| | 5486 | 5516 | 5546 | 5576 | | | | |
| | 5487 | 5517 | 5547 | 5577 | | | | |
| | 5488 | 5518 | 5548 | 5578 | | | | |
| | 5489 | 5519 | 5549 | 5579 | | | | |
| | 5490 | 5520 | 5550 | 5580 | | | | |
| | 5491 | 5521 | 5551 | 5581 | | | | |
| | 5492 | 5522 | 5552 | 5582 | | | | |
| | 5493 | 5523 | 5553 | 5583 | | | | |

# APPENDIX O

## Attachment 2 (continued)

## Gross Pathology Observations – Animal Cross Reference

Removal Reason: All of those selected

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| SEMINAL VESICLES; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (-) | (-) | (-) | (-) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5574 | | | | |
| | 5485 | 5515 | 5545 | 5575 | | | | |
| | 5486 | 5518 | 5546 | 5577 | | | | |
| | 5487 | 5517 | 5547 | 5578 | | | | |
| | 5488 | 5518 | 5548 | 5579 | | | | |
| | 5489 | 5519 | 5549 | 5580 | | | | |
| | 5490 | 5520 | 5550 | 5581 | | | | |
| | 5491 | 5521 | 5551 | 5582 | | | | |
| | 5492 | 5522 | 5552 | | | | | |
| | 5493 | | 5553 | | | | | |
| Small; minimal | | 5523 | | | | | | |
| Small | | | | 5576 | | | | |
| Enlarged; minimal | | | | 5583 | | | | |
| SPINAL CORD; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5574 | 5474 | 5505 | 5534 | 5564 |
| | 5485 | 5515 | 5545 | 5575 | 5475 | 5506 | 5535 | 5565 |
| | 5486 | 5516 | 5546 | 5576 | 5476 | 5507 | 5536 | 5566 |
| | 5487 | 5517 | 5547 | 5577 | 5477 | 5508 | 5537 | 5567 |
| | 5488 | 5518 | 5548 | 5578 | 5478 | 5509 | 5538 | 5568 |
| | 5489 | 5519 | 5549 | 5579 | 5479 | 5510 | 5539 | 5569 |
| | 5490 | 5520 | 5550 | 5580 | 5480 | 5511 | 5540 | 5570 |
| | 5491 | 5521 | 5551 | 5581 | 5481 | 5512 | 5541 | 5571 |
| | 5492 | 5522 | 5552 | 5582 | 5482 | 5513 | 5542 | 5572 |
| | 5493 | 5523 | 5553 | 5583 | 5483 | | 5543 | 5573 |
| SPLEEN; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5574 | 5474 | 5505 | 5534 | 5564 |
| | 5485 | 5515 | 5545 | 5575 | 5475 | 5506 | 5535 | 5565 |
| | 5486 | 5516 | 5546 | 5576 | 5476 | 5507 | 5536 | 5566 |
| | 5487 | 5517 | 5547 | 5577 | 5477 | 5508 | 5537 | 5567 |

# APPENDIX O

## Attachment 2 (continued)

## Gross Pathology Observations – Animal Cross Reference

Removal Reason: All of those selected

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| SPLEEN; (continued) | | | | | | | | |
| No Visible Lesions (continued) | 5488<br>5489<br>5490<br>5491<br>5492<br>5493 | 5518<br>5519<br>5520<br>5521<br>5522<br>5523 | 5548<br>5549<br>5551<br>5552<br>5553 | 5578<br>5579<br>5580<br>5581<br>5582<br>5583 | 5478<br>5479<br>5480<br>5481<br>5482<br>5483 | 5509<br>5511<br>5512<br>5513 | 5538<br>5539<br>5540<br>5541<br>5543 | 5568<br>5569<br>5570<br>5571<br>5572<br>5573 |
| Discoloration; dark | | | | | | 5510 | | |
| Enlarged; minimal | | | 5550 | | | | 5542 | |
| STOMACH; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484<br>5485<br>5486<br>5487<br>5466<br>5469<br>5490<br>5491<br>5492<br>5493 | 5514<br>5515<br>5516<br>5517<br>5518<br>5519<br>5520<br>5521<br>5522<br>5523 | 5544<br>5545<br>5546<br>5547<br>5548<br>5549<br>5550<br>5551<br>5552<br>5553 | 5574<br>5575<br>5576<br>5577<br>5578<br>5579<br>5580<br>5581<br>5582<br>5583 | 5474<br>5475<br>5476<br>5477<br>5478<br>5479<br>5480<br>5481<br>5482<br>5483 | 5505<br>5506<br>5507<br>5508<br>5509<br>5510<br>5511<br>5512<br>5513 | 5534<br>5535<br>5536<br>5537<br>5538<br>5539<br>5540<br>5541<br>5542<br>5543 | 5564<br>5565<br>5566<br>5567<br>5568<br>5569<br>5570<br>5571<br>5572<br>5573 |
| TESTES; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (-) | (-) | (-) | (-) |
| No Visible Lesions | 5484<br>5465<br>5486<br>5487<br>5488<br>5489<br>5490<br>5491<br>5492<br>5493 | 5514<br>5515<br>5516<br>5517<br>5518<br>5519<br>5520<br>5521<br>5522<br>5523 | 5544<br>5545<br>5546<br>5547<br>5548<br>5549<br>5550<br>5551<br>5552<br>5553 | 5574<br>5575<br>5576<br>5577<br>5578<br>5579<br>5580<br>5562<br>5583 | | | | |
| Discoloration; hemorrhagic; unilateral | | | | 5581 | | | | |

# APPENDIX O

## Attachment 2 (continued)

## Gross Pathology Observations – Animal Cross Reference

Removal Reason: All of those selected

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| THYMUS; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5485<br>5486<br>5487<br>5488<br>5489<br>5490<br>5491<br>5492<br>5493 | 5514<br>5515<br>5516<br>5517<br>5518<br>5519<br>5520<br>5521<br>5522<br>5523 | 5544<br>5545<br>5546<br>5549<br>5550<br>5551 | 5574<br>5575<br>5577<br>5579<br>5582 | 5474<br>5475<br>5476<br>5477<br>5478<br>5479<br>5480<br>5481<br>5482<br>5483 | 5505<br>5507<br>5508<br>5509<br>5510<br>5511<br>5512 | 5534<br>5535<br>5536<br>5537<br>5538<br>5539<br>5540<br>5541<br>5542<br>5543 | 5564<br>5565<br>5566<br>5567<br>5568<br>5569<br>5570<br>5571<br>5572<br>5573 |
| Discoloration | | | | | | 5506 | | |
| Discoloration; dark; multiple; minimal | | | | 5581 | | | | |
| Discoloration; red; unilateral; multifocal | 5484 | | | | | | | |
| Discoloration; red; multifocal | | | | | | 5513 | | |
| Discoloration; red; multiple | | | 5547 | | | | | |
| Discoloration; few | | | 5552 | | | | | |
| Enlarged | | | | | | 5513 | | |
| Small; minimal | | | | 5576 | | | | |
| Small | | | 5547<br>5548<br>5553 | 5576<br>5580<br>5583 | | | | |
| THYROID GLANDS; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484<br>5485<br>5488 | 5514<br>5515<br>5516 | 5544<br>5545<br>5548 | 5574<br>5575<br>5576 | 5474<br>5475<br>5476 | 5505<br>5506<br>5507 | 5534<br>5535<br>5536 | 5564<br>5565<br>5566 |

# APPENDIX O

## Attachment 2 (continued)

## Gross Pathology Observations – Animal Cross Reference

Removal Reason: All of those selected

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| THYROID GLANDS; (continued) | | | | | | | | |
| No Visible Lesions (continued) | 5487 | 5517 | 5547 | 5577 | 5477 | 5508 | 5537 | 5567 |
| | 5488 | 5518 | 5548 | 5578 | 5478 | 5509 | 5538 | 5588 |
| | 5489 | 5519 | 5549 | 5579 | 5479 | 5510 | 5539 | 5589 |
| | 5490 | 5520 | 5550 | 5580 | 5460 | 5511 | 5540 | 5570 |
| | 5491 | 5521 | 5551 | 5581 | 5481 | 5512 | 5541 | 5571 |
| | 5492 | 5522 | 5552 | 5582 | 5482 | 5513 | 5542 | 5572 |
| | 5493 | 5523 | 5553 | 5583 | 5483 | | 5543 | 5573 |
| TRACHEA; | | | | | | | | |
| Submitted | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| No Visible Lesions | 5484 | 5514 | 5544 | 5574 | 5474 | 5505 | 5534 | 5564 |
| | 5485 | 5515 | 5545 | 5575 | 5475 | 5506 | 5535 | 5565 |
| | 5486 | 5518 | 5546 | 5576 | 5476 | 5507 | 5536 | 5566 |
| | 5487 | 5517 | 5547 | 5577 | 5477 | 5508 | 5537 | 5567 |
| | 5488 | 5518 | 5548 | 5578 | 5478 | 5509 | 5538 | 5568 |
| | 5489 | 5519 | 5549 | 5579 | 5479 | 5510 | 5539 | 5589 |
| | 5490 | 5520 | 5550 | 5580 | 5480 | 5511 | 5540 | 5570 |
| | 5491 | 5521 | 5551 | 5581 | 5481 | 5512 | 5541 | 5571 |
| | 5492 | 5522 | 5552 | 5582 | 5482 | 5513 | 5542 | 5572 |
| | 5493 | 5523 | 5553 | 5583 | 5483 | | 5543 | 5573 |
| URINARY BLADDER; | | | | | | | | |
| Submitted | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| No Visible Lesions | 5484 | | | 5574 | 5474 | | | 5564 |
| | 5485 | | | 5575 | 5475 | | | 5565 |
| | 5486 | | | 5576 | 5476 | | | 5566 |
| | 5487 | | | 5577 | 5477 | | | 5567 |
| | 5488 | | | 5578 | 5478 | | | 5568 |
| | 5489 | | | 5579 | 5479 | | | 5589 |
| | 5490 | | | 5580 | 5480 | | | 5570 |
| | 5491 | | | 5581 | 5481 | | | 5571 |
| | 5492 | | | 5582 | 5482 | | | 5572 |
| | 5493 | | | 5583 | 5483 | | | 5573 |
| UTERUS; | | | | | | | | |
| Submitted | (-) | (-) | (-) | (-) | (10) | (9) | (10) | (10) |
| No Visible Lesions | | | | | 5474 | 5505 | 5534 | 5564 |
| | | | | | 5475 | 5506 | 5535 | 5565 |
| | | | | | 5476 | 5507 | 5536 | 5586 |

# APPENDIX O

## Attachment 3

## Intergroup Comparison of Histopathology Observations

| Observations: Neo-Plastic and Non Neo-Plastic | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| Removal Reasons: All of those SELECTED | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| ADRENAL GLANDS; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| BONE MARROW, STERNUM; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| BRAIN; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| EPIDIDYMIDES; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (-) | (-) | (-) | (-) |
| Within Normal Limits | 10 | 0 | 0 | 9 | - | - | - | - |
| Immature; spermatid | (0) | (0) | (0) | (1) | (-) | (-) | (-) | (-) |
| minimal | 0 | 0 | 0 | 1 | - | - | - | - |
| HEART; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 9 | 0 | 0 | 9 | 10 | 0 | 0 | 9 |
| Hyperplasia; atrium; endocardium | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (1) |
| mild | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Inflammation; chronic; focal | (1) | (0) | (0) | (1) | (0) | (0) | (0) | (0) |
| minimal | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| INTESTINE, CECUM; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| INTESTINE, COLON; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| INTESTINE, DUODENUM; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |

# APPENDIX O

## Attachment 3 (continued)

## Intergroup Comparison of Histopathology Observations

| Observations: Neo-Plastic and Non Neo-Plastic | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| Removal Reasons: All of those SELECTED | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| INTESTINE, ILEUM; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| INTESTINE, JEJUNUM; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| KIDNEYS; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 5 | 0 | 0 | 5 | 4 | 0 | 0 | 7 |
| Hyperplasia; tubular; focal | (0) | (0) | (0) | (1) | (0) | (0) | (0) | (0) |
| moderate | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Infarction; focal | (0) | (0) | (0) | (1) | (0) | (0) | (0) | (0) |
| moderate | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Inflammation; chronic; focal | (3) | (0) | (0) | (1) | (3) | (0) | (0) | (1) |
| minimal | 3 | 0 | 0 | 1 | 3 | 0 | 0 | 1 |
| Basophilia; tubular; focal | (4) | (0) | (0) | (5) | (3) | (0) | (0) | (2) |
| minimal | 3 | 0 | 0 | 4 | 3 | 0 | 0 | 2 |
| mild | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| LIVER; | | | | | | | | |
| Examined | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| Within Normal Limits | 1 | 2 | 0 | 0 | 2 | 0 | 0 | 0 |
| Hypertrophy; centrilobular | (0) | (1) | (8) | (8) | (0) | (0) | (8) | (10) |
| minimal | 0 | 1 | 7 | 3 | 0 | 0 | 4 | 0 |
| mild | 0 | 0 | 1 | 5 | 0 | 0 | 4 | 10 |
| Inflammation; chronic; multifocal | (9) | (8) | (8) | (1) | (7) | (9) | (6) | (4) |
| minimal | 8 | 7 | 8 | 1 | 8 | 9 | 4 | 4 |
| mild | 1 | 1 | 0 | 0 | 1 | 0 | 2 | 0 |
| Inflammation; chronic; periportal | (0) | (0) | (0) | (9) | (0) | (0) | (0) | (0) |
| minimal | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 |
| mild | 0 | 0 | 0 | 5 | 0 | 0 | 0 | 0 |
| Hyperplasia, Bile Duct, Assoc W Pps | (0) | (0) | (0) | (6) | (0) | (0) | (0) | (0) |
| minimal | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 |
| mild | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 |
| moderate | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |

# APPENDIX O

## Attachment 3 (continued)

## Intergroup Comparison of Histopathology Observations

| Observations: Neo-Plastic and Non Neo-Plastic | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| Removal Reasons: All of those SELECTED | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| LIVER; (continued) | | | | | | | | |
| Vacuolation; hepatocellular; centrilobular | (0) | (1) | (0) | (0) | (0) | (0) | (0) | (0) |
| mild | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Vacuolation; hepatocellular; periportal | (2) | (0) | (2) | (3) | (5) | (4) | (7) | (10) |
| minimal | 1 | 0 | 1 | 0 | 3 | 4 | 2 | 0 |
| mild | 1 | 0 | 1 | 3 | 2 | 0 | 3 | 6 |
| moderate | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 4 |
| Protoporphyrinosis | (0) | (0) | (0) | (9) | (0) | (0) | (0) | (0) |
| minimal | 0 | 0 | 0 | 5 | 0 | 0 | 0 | 0 |
| mild | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| moderate | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 |
| LUNGS; | | | | | | | | |
| Examined | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| Within Normal Limits | 3 | 6 | 2 | 2 | 7 | 4 | 7 | 6 |
| Hemorrhage; focal | (2) | (0) | (1) | (1) | (0) | (1) | (0) | (0) |
| minimal | 2 | 0 | 1 | 1 | 0 | 1 | 0 | 0 |
| Hyperplasia; lymphoid tissue | (0) | (1) | (1) | (0) | (0) | (1) | (1) | (0) |
| mild | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 0 |
| Inflammation; acute; focal | (1) | (0) | (0) | (0) | (0) | (1) | (0) | (0) |
| minimal | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Inflammation; chronic; focal | (1) | (0) | (0) | (0) | (0) | (0) | (1) | (0) |
| minimal | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Inflammation; chronic; multifocal | (1) | (0) | (0) | (1) | (0) | (0) | (0) | (0) |
| minimal | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Histocytosis | (4) | (4) | (8) | (6) | (3) | (3) | (2) | (5) |
| minimal | 4 | 4 | 4 | 6 | 3 | 3 | 1 | 5 |
| mild | 0 | 0 | 4 | 0 | 0 | 0 | 1 | 0 |
| LYMPH NODE, MEDIASTINAL; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| LYMPH NODE, MESENTERIC; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |

# APPENDIX O

## Attachment 3 (continued)

## Intergroup Comparison of Histopathology Observations

| Observations: Neo-Plastic and Non Neo-Plastic | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| Removal Reasons: All of those SELECTED | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| NERVE, SCIATIC; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| OVARIES; | | | | | | | | |
| Examined | (-) | (-) | (-) | (-) | (10) | (0) | (0) | (10) |
| Within Normal Limits | - | - | - | - | 9 | 0 | 0 | 9 |
| Cyst; corpus luteum | - | - | - | - | 1 | 0 | 0 | 1 |
| PROSTATE GLAND; | | | | | | | | |
| Examined | (10) | (10) | (10) | (10) | (-) | (-) | (-) | (-) |
| Within Normal Limits | 8 | 3 | 5 | 3 | - | - | - | - |
| Inflammation; chronic | (2) | (8) | (5) | (7) | (-) | (-) | (-) | (-) |
| minimal | 0 | 3 | 5 | 1 | - | - | - | - |
| mild | 1 | 2 | 0 | 6 | - | - | - | - |
| moderate | 1 | 1 | 0 | 0 | - | - | - | - |
| Inflammation; chronic-active | (0) | (1) | (0) | (0) | (-) | (-) | (-) | (-) |
| marked | 0 | 1 | 0 | 0 | - | - | - | - |
| Necrosis; single cell | (1) | (0) | (0) | (1) | (-) | (-) | (-) | (-) |
| minimal | 1 | 0 | 0 | 1 | - | - | - | - |
| SEMINAL VESICLES; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (-) | (-) | (-) | (-) |
| Within Normal Limits | 10 | 0 | 0 | 9 | - | - | - | - |
| Atrophy; unilateral | (0) | (0) | (0) | (1) | (-) | (-) | (-) | (-) |
| mild | 0 | 0 | 0 | 1 | - | - | - | - |
| SPINAL CORD; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| SPLEEN; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| STOMACH; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |

# APPENDIX O

## Attachment 2 (continued)

## Gross Pathology Observations – Animal Cross Reference

Removal Reason: All of those selected

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| UTERUS; (continued) | | | | | | | | |
| No Visible Lesions (continued) ..... | | | | | 5477 | 5508 | 5537 | 5567 |
| | | | | | 5478 | 5509 | 5538 | 5568 |
| | | | | | 5479 | 5510 | 5539 | 5569 |
| | | | | | 5480 | 5511 | 5540 | 5570 |
| | | | | | 5481 | 5512 | 5541 | 5571 |
| | | | | | 5482 | 5513 | 5542 | 5572 |
| | | | | | 5483 | | 5543 | 5573 |

# APPENDIX O

## Attachment 3 (continued)

## Intergroup Comparison of Histopathology Observations

| Observations: Neo-Plastic and Non Neo-Plastic | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| Removal Reasons: All of those SELECTED | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| STOMACH; (continued) | | | | | | | | |
| Within Normal Limits | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| TESTES; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (-) | (-) | (-) | (-) |
| Within Normal Limits | 10 | 0 | 0 | 9 | - | - | - | - |
| Degeneration; spermatid | (0) | (0) | (0) | (1) | (-) | (-) | (-) | (-) |
| minimal | 0 | 0 | 0 | 1 | - | - | - | - |
| Cyst; seminiferous tubule | 0 | 0 | 0 | 1 | - | - | - | - |
| THYMUS; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| THYROID GLANDS; | | | | | | | | |
| Examined | (10) | (10) | (10) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 7 | 7 | 2 | 1 | 7 | 0 | 0 | 6 |
| Cyst; ultimobranchial | 2 | 3 | 0 | 1 | 2 | 0 | 0 | 3 |
| Ectopic Thymus | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Hypertrophy; follicular | (1) | (0) | (8) | (9) | (0) | (0) | (0) | (1) |
| minimal | 1 | 0 | 5 | 1 | 0 | 0 | 0 | 1 |
| mild | 0 | 0 | 3 | 8 | 0 | 0 | 0 | 0 |
| TRACHEA; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| URINARY BLADDER; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 9 |
| Inflammation; chronic; focal | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (1) |
| minimal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| UTERUS; | | | | | | | | |
| Examined | (-) | (-) | (-) | (-) | (10) | (0) | (0) | (10) |
| Within Normal Limits | - | - | - | - | 9 | 0 | 0 | 10 |
| Inflammation; acute; diffuse | (-) | (-) | (-) | (-) | (1) | (0) | (0) | (0) |

# APPENDIX O

## Attachment 3 (continued)

## Intergroup Comparison of Histopathology Observations

Observations: Neo-Plastic and Non Neo-Plastic
Removal Reasons: All of those SELECTEO

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| Number of Animals on Study : | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 |
| Number of Animals Completed: | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| UTERUS; (continued) | | | | | | | | |
| mild ..... | - | - | - | - | 1 | 0 | 0 | 0 |

# APPENDIX O

## Attachment 4

## Histopathology Observations – Animal Cross Reference

Removal Reason: All of those selected

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| ADRENAL GLANDS; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 5484 | | | 5574 | 5474 | | | 5564 |
| | 5485 | | | 5575 | 5475 | | | 5565 |
| | 5486 | | | 5576 | 5476 | | | 5566 |
| | 5487 | | | 5577 | 5477 | | | 5567 |
| | 5488 | | | 5578 | 5478 | | | 5568 |
| | 5489 | | | 5579 | 5479 | | | 5569 |
| | 5490 | | | 5580 | 5480 | | | 5570 |
| | 5491 | | | 5581 | 5481 | | | 5571 |
| | 5492 | | | 5582 | 5482 | | | 5572 |
| | 5493 | | | 5583 | 5483 | | | 5573 |
| BONE MARROW, STERNUM; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 5484 | | | 5574 | 5474 | | | 5564 |
| | 5485 | | | 5575 | 5475 | | | 5565 |
| | 5486 | | | 5576 | 5476 | | | 5566 |
| | 5487 | | | 5577 | 5477 | | | 5567 |
| | 5488 | | | 5578 | 5478 | | | 5568 |
| | 5489 | | | 5579 | 5479 | | | 5569 |
| | 5490 | | | 5580 | 5480 | | | 5570 |
| | 5491 | | | 5581 | 5481 | | | 5571 |
| | 5492 | | | 5582 | 5482 | | | 5572 |
| | 5493 | | | 5583 | 5483 | | | 5573 |
| BRAIN; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 5484 | | | 5574 | 5474 | | | 5564 |
| | 5485 | | | 5575 | 5475 | | | 5565 |
| | 5486 | | | 5576 | 5476 | | | 5566 |
| | 5487 | | | 5577 | 5477 | | | 5567 |
| | 5488 | | | 5578 | 5478 | | | 5568 |
| | 5489 | | | 5579 | 5479 | | | 5569 |
| | 5490 | | | 5580 | 5480 | | | 5570 |
| | 5491 | | | 5581 | 5481 | | | 5571 |
| | 5492 | | | 5582 | 5482 | | | 5572 |
| | 5493 | | | 5563 | 5483 | | | 5573 |

# APPENDIX O

## Attachment 4 (continued)

## Histopathology Observations – Animal Cross Reference

Removal Reason: All of those selected

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| EPIDIDYMIDES; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (-) | (-) | (-) | (-) |
| Within Normal Limits | 5484<br>5485<br>5486<br>5487<br>5488<br>5489<br>5490<br>5491<br>5492<br>5493 | | | 5574<br>5575<br>5576<br>5577<br>5578<br>5579<br>5580<br>5581<br>5582 | | | | |
| spermatid; Immature; minimal | | | | 5583 | | | | |
| HEART; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 5484<br>5486<br>5487<br>5488<br>5489<br>5490<br>5491<br>5492<br>5493 | | | 5574<br>5575<br>5576<br>5577<br>5579<br>5580<br>5581<br>5582<br>5583 | 5474<br>5475<br>5476<br>5477<br>5478<br>5479<br>5480<br>5481<br>5482<br>5483 | | | 5584<br>5565<br>5566<br>5567<br>5568<br>5569<br>5570<br>5571<br>5572 |
| Inflammation; chronic; focal; minimal | 5485 | | | 5578 | | | | |
| atrium; Hyperplasia; endocardium; mild | | | | | | | | 5573 |
| INTESTINE, CECUM; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 5484<br>5485<br>5486 | | | 5574<br>5575<br>5576 | 5474<br>5475<br>5476 | | | 5564<br>5565<br>5566 |

# APPENDIX O

## Attachment 4 (continued)

## Histopathology Observations – Animal Cross Reference

Removal Reason: All of those selected

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| INTESTINE, CECUM; (continued) | | | | | | | | |
| Within Normal Limits (continued) | 5487 | | | 5577 | 5477 | | | 5567 |
| | 5488 | | | 5578 | 5478 | | | 5568 |
| | 5489 | | | 5579 | 5479 | | | 5569 |
| | 5490 | | | 5580 | 5480 | | | 5570 |
| | 5491 | | | 5581 | 5481 | | | 5571 |
| | 5492 | | | 5582 | 5482 | | | 5572 |
| | 5493 | | | 5583 | 5483 | | | 5573 |
| INTESTINE, COLON; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 5484 | | | 5574 | 5474 | | | 5564 |
| | 5485 | | | 5575 | 5475 | | | 5565 |
| | 5486 | | | 5576 | 5476 | | | 5566 |
| | 5487 | | | 5577 | 5477 | | | 5567 |
| | 5488 | | | 5578 | 5478 | | | 5568 |
| | 5489 | | | 5579 | 5479 | | | 5569 |
| | 5490 | | | 5580 | 5480 | | | 5570 |
| | 5491 | | | 5581 | 5481 | | | 5571 |
| | 5492 | | | 5582 | 5482 | | | 5572 |
| | 5493 | | | 5583 | 5483 | | | 5573 |
| INTESTINE, DUODENUM; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 5484 | | | 5574 | 5474 | | | 5564 |
| | 5485 | | | 5575 | 5475 | | | 5565 |
| | 5486 | | | 5576 | 5476 | | | 5566 |
| | 5487 | | | 5577 | 5477 | | | 5567 |
| | 5488 | | | 5578 | 5478 | | | 5568 |
| | 5489 | | | 5579 | 5479 | | | 5569 |
| | 5490 | | | 5580 | 5480 | | | 5570 |
| | 5491 | | | 5581 | 5481 | | | 5571 |
| | 5492 | | | 5582 | 5482 | | | 5572 |
| | 5493 | | | 5583 | 5483 | | | 5573 |
| INTESTINE, ILEUM; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 5484 | | | 5574 | 5474 | | | 5564 |
| | 5485 | | | 5575 | 5475 | | | 5565 |
| | 5486 | | | 5576 | 5476 | | | 5566 |

# APPENDIX O

## Attachment 4 (continued)

## Histopathology Observations – Animal Cross Reference

Removal Reason: All of those selected

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| INTESTINE, ILEUM; (continued) | | | | | | | | |
| Within Normal Limits (continued) | 5487 | | | 5577 | 5477 | | | 5587 |
| | 5488 | | | 5578 | 5478 | | | 5568 |
| | 5489 | | | 5579 | 5479 | | | 5569 |
| | 5490 | | | 5580 | 5480 | | | 5570 |
| | 5491 | | | 5581 | 5481 | | | 5571 |
| | 5492 | | | 5582 | 5482 | | | 5572 |
| | 5493 | | | 5583 | 5483 | | | 5573 |
| INTESTINE, JEJUNUM; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 5484 | | | 5574 | 5474 | | | 5564 |
| | 5485 | | | 5575 | 5475 | | | 5565 |
| | 5486 | | | 5576 | 5476 | | | 5566 |
| | 5487 | | | 5577 | 5477 | | | 5567 |
| | 5488 | | | 5578 | 5478 | | | 5568 |
| | 5489 | | | 5579 | 5479 | | | 5589 |
| | 5490 | | | 5580 | 5480 | | | 5570 |
| | 5491 | | | 5581 | 5481 | | | 5571 |
| | 5492 | | | 5582 | 5482 | | | 5572 |
| | 5493 | | | 5583 | 5483 | | | 5573 |
| KIDNEYS; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 5484 | | | 5574 | 5476 | | | 5565 |
| | 5485 | | | 5575 | 5481 | | | 5566 |
| | 5486 | | | 5576 | 5482 | | | 5567 |
| | 5490 | | | 5579 | 5483 | | | 5568 |
| | 5491 | | | 5580 | | | | 5569 |
| | | | | | | | | 5570 |
| | | | | | | | | 5572 |
| Hyperplasia; tubular; focal; moderate | | | | 5581 | | | | |
| Infarction; focal; moderate | | | | 5581 | | | | |

# APPENDIX O

## Attachment 4 (continued)

## Histopathology Observations – Animal Cross Reference

Removal Reason: All of those selected

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| KIDNEYS; (continued) | | | | | | | | |
| Inflammation; chronic; focal; | | | | | | | | |
| minimal | 5489<br>5492<br>5493 | | | 5582 | 5474<br>5475<br>5479 | | | 5564 |
| Basophilia; tubular; focal; | | | | | | | | |
| minimal | 5486<br>5487<br>5492 | | | 5577<br>5578<br>5582<br>5583 | 5477<br>5478<br>5480 | | | 5571<br>5573 |
| mild | 5489 | | | 5581 | | | | |
| LIVER; | | | | | | | | |
| Examined | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| Within Normal Limits | 5486 | 5518<br>5522 | | | 5476<br>5482 | | | |
| Inflammation; chronic; multifocal; | | | | | | | | |
| minimal | 5484<br>5485<br>5487<br>5488<br>5489<br>5490<br>5491<br>5493 | 5515<br>5516<br>5517<br>5519<br>5520<br>5521<br>5523 | 5545<br>5546<br>5547<br>5548<br>5549<br>5550<br>5552<br>5553 | 5583 | 5475<br>5477<br>5478<br>5480<br>5481<br>5483 | 5505<br>5506<br>5507<br>5508<br>5509<br>5510<br>5511<br>5512<br>5513 | 5534<br>5535<br>5537<br>5538 | 5568<br>5571<br>5572<br>5573 |
| mild | 5492 | 5514 | | | 5479 | | 5542<br>5543 | |
| Hyperplasia, Bile Duct, Assoc W Pps; | | | | | | | | |
| minimal | | | | 5575<br>5578<br>5582 | | | | |

# APPENDIX O

## Attachment 4 (continued)

## Histopathology Observations – Animal Cross Reference

Removal Reason: All of those selected

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| LIVER; (continued) | | | | | | | | |
| mild | | | | 5577<br>5580<br>5581 | | | | |
| moderate | | | | 5574<br>5576 | | | | |
| Protoporphyrinosis; | | | | | | | | |
| minimal | | | | 5575<br>5577<br>5578<br>5579<br>5582 | | | | |
| mild | | | | 5581 | | | | |
| moderate | | | | 5574<br>5576<br>5580 | | | | |
| centrilobular; Hypertrophy; | | | | | | | | |
| minimal | | 5517 | 5544<br>5546<br>5547<br>5548<br>5549<br>5550<br>5551 | 5581<br>5582<br>5583 | | | 5534<br>5536<br>5539<br>5540 | |
| mild | | | 5545 | 5574<br>5576<br>5577<br>5578<br>5579 | | | 5535<br>5541<br>5542<br>5543 | 5564<br>5565<br>5566<br>5567<br>5568<br>5569<br>5570<br>5571<br>5572<br>5573 |

# APPENDIX O

## Attachment 4 (continued)

## Histopathology Observations – Animal Cross Reference

Removal Reason: All of those selected

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| LIVER; (continued) | | | | | | | | |
| centrilobular; Vacuolation; hepatocellular; | | | | | | | | |
| mild | | 5523 | | | | | | |
| periportal; Inflammation; chronic; | | | | | | | | |
| minimal | | | | 5575<br>5578<br>5579<br>5582 | | | | |
| mild | | | | 5574<br>5578<br>5577<br>5580<br>5581 | | | | |
| periportal; Vacuolation; hepatocellular; | | | | | | | | |
| minimal | 5484 | | 5546 | | 5475<br>5477<br>5478 | 5507<br>5509<br>5510<br>5511 | 5535<br>5536 | |
| mild | 5492 | | 5549 | 5577<br>5579<br>5580 | 5474<br>5479 | | 5534<br>5538<br>5543 | 5566<br>5568<br>5570<br>5571<br>5572<br>5573 |
| moderate | | | | | | | 5537<br>5542 | 5564<br>5565<br>5567<br>5569 |
| LUNGS; | | | | | | | | |
| Examined | (10) | (10) | (10) | (10) | (10) | (9) | (10) | (10) |
| Within Normal Limits | 5485<br>5487<br>5489 | 5517<br>5518<br>5519<br>5521 | 5545<br>5553 | 5575<br>5581 | 5474<br>5476<br>5477<br>5480 | 5508<br>5511<br>5512<br>5513 | 5534<br>5535<br>5536<br>5538 | 5564<br>5565<br>5567<br>5570 |

# APPENDIX O

## Attachment 4 (continued)

## Histopathology Observations – Animal Cross Reference

Removal Reason: All of those selected

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| LUNGS; (continued) | | | | | | | | |
| Within Normal Limits (continued) | | 5522<br>5523 | | | 5481<br>5482<br>5483 | | 5540<br>5541<br>5542 | 5573 |
| Hemorrhage; focal; minimal | 5484<br>5493 | | 5546 | 5583 | | 5509 | | |
| Inflammation; acute; focal; minimal | 5484 | | | | | 5505 | | |
| Inflammation; chronic; focal; minimal | 5493 | | | | | | 5539 | |
| Inflammation; chronic; multifocal; minimal | 5491 | | | 5576 | | | | |
| Histocytosis; minimal | 5486<br>5488<br>5490<br>5492 | 5514<br>5515<br>5516<br>5520 | 5548<br>5549<br>5551<br>5552 | 5574<br>5576<br>5577<br>5578<br>5579<br>5580<br>5582<br>5583 | 5475<br>5478<br>5479 | 5505<br>5506<br>5510 | 5537 | 5568<br>5568<br>5569<br>5571<br>5572 |
| mild | | | 5544<br>5546<br>5547<br>5550 | | | | 5539 | |
| lymphoid tissue; Hyperplasia; mild | | 5514 | 5549 | | | 5507 | 5543 | |
| LYMPH NODE, MEDIASTINAL; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 5484<br>5485 | | | 5574<br>5575 | 5474<br>5475 | | | 5564<br>5565 |

# APPENDIX O

## Attachment 4 (continued)

## Histopathology Observations – Animal Cross Reference

Removal Reason: All of those selected

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| LYMPH NODE, MEDIASTINAL; (continued) | | | | | | | | |
| Within Normal Limits (continued) | 5486 | | | 5576 | 5476 | | | 5566 |
| | 5487 | | | 5577 | 5477 | | | 5567 |
| | 5488 | | | 5578 | 5478 | | | 5568 |
| | 5489 | | | 5579 | 5479 | | | 5569 |
| | 5490 | | | 5580 | 5480 | | | 5570 |
| | 5491 | | | 5581 | 5481 | | | 5571 |
| | 5492 | | | 5582 | 5482 | | | 5572 |
| | 5493 | | | 5583 | 5483 | | | 5573 |
| LYMPH NODE, MESENTERIC; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 5484 | | | 5574 | 5474 | | | 5564 |
| | 5485 | | | 5575 | 5475 | | | 5565 |
| | 5486 | | | 5576 | 5476 | | | 5566 |
| | 5487 | | | 5577 | 5477 | | | 5567 |
| | 5488 | | | 5578 | 5478 | | | 5568 |
| | 5489 | | | 5579 | 5479 | | | 5569 |
| | 5490 | | | 5580 | 5480 | | | 5570 |
| | 5491 | | | 5581 | 5481 | | | 5571 |
| | 5492 | | | 5582 | 5482 | | | 5572 |
| | 5493 | | | 5583 | 5483 | | | 5573 |
| NERVE, SCIATIC; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 5484 | | | 5574 | 5474 | | | 5564 |
| | 5485 | | | 5575 | 5475 | | | 5565 |
| | 5486 | | | 5576 | 5476 | | | 5566 |
| | 5487 | | | 5577 | 5477 | | | 5567 |
| | 5488 | | | 5578 | 5478 | | | 5568 |
| | 5489 | | | 5579 | 5479 | | | 5569 |
| | 5490 | | | 5580 | 5480 | | | 5570 |
| | 5491 | | | 5581 | 5481 | | | 5571 |
| | 5492 | | | 5582 | 5482 | | | 5572 |
| | 5493 | | | 5583 | 5483 | | | 5573 |
| OVARIES; | | | | | | | | |
| Examined | (-) | (-) | (-) | (-) | (10) | (0) | (0) | (10) |
| Within Normal Limits | | | | | 5474 | | | 5564 |
| | | | | | 5475 | | | 5566 |

# APPENDIX O

## Attachment 4 (continued)

## Histopathology Observations – Animal Cross Reference

Removal Reason: All of those selected

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| OVARIES; (continued) | | | | | | | | |
| Within Normal Limits (continued) | | | | | 5476<br>5477<br>5479<br>5480<br>5481<br>5482<br>5483 | | | 5567<br>5568<br>5569<br>5570<br>5571<br>5572<br>5573 |
| corpus luteum; Cyst | | | | | 5478 | | | 5565 |
| PROSTATE GLAND; | | | | | | | | |
| Examined | (10) | (10) | (10) | (10) | (-) | (-) | (-) | (-) |
| Within Normal Limits | 5484<br>5485<br>5486<br>5487<br>5488<br>5491<br>5492<br>5493 | 5517<br>5520<br>5523 | 5544<br>5547<br>5549<br>5551<br>5553 | 5576<br>5577<br>5580 | | | | |
| Inflammation; chronic; | | | | | | | | |
| minimal | | 5514<br>5516<br>5521 | 5545<br>5546<br>5548<br>5550<br>5552 | 5581 | | | | |
| mild | 5489 | 5515<br>5519 | | 5574<br>5575<br>5578<br>5579<br>5582<br>5583 | | | | |
| moderate | 5490 | 5522 | | | | | | |

# APPENDIX O

## Attachment 4 (continued)

## Histopathology Observations – Animal Cross Reference

Removal Reason: All of those selected

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| PROSTATE GLAND; (continued) | | | | | | | | |
| Inflammation; chronic-active; | | | | | | | | |
| marked | | 5518 | | | | | | |
| Necrosis; single cell; | | | | | | | | |
| minimal | 5490 | | | 5583 | | | | |
| SEMINAL VESICLES; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (-) | (-) | (-) | (-) |
| Within Normal Limits | 5484 | | | 5574 | | | | |
| | 5485 | | | 5575 | | | | |
| | 5486 | | | 5576 | | | | |
| | 5487 | | | 5577 | | | | |
| | 5488 | | | 5578 | | | | |
| | 5489 | | | 5579 | | | | |
| | 5490 | | | 5580 | | | | |
| | 5491 | | | 5581 | | | | |
| | 5492 | | | 5582 | | | | |
| | 5493 | | | | | | | |
| Atrophy; unilateral; | | | | | | | | |
| mild | | | | 5583 | | | | |
| SPINAL CORD; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 5484 | | | 5574 | 5474 | | | 5564 |
| | 5485 | | | 5575 | 5475 | | | 5565 |
| | 5486 | | | 5576 | 5476 | | | 5566 |
| | 5487 | | | 5577 | 5477 | | | 5567 |
| | 5488 | | | 5578 | 5478 | | | 5568 |
| | 5489 | | | 5579 | 5479 | | | 5569 |
| | 5490 | | | 5580 | 5480 | | | 5570 |
| | 5491 | | | 5581 | 5481 | | | 5571 |
| | 5492 | | | 5582 | 5482 | | | 5572 |
| | 5493 | | | 5583 | 5483 | | | 5573 |
| SPLEEN; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 5484 | | | 5574 | 5474 | | | 5564 |
| | 5485 | | | 5575 | 5475 | | | 5565 |

# APPENDIX O

## Attachment 4 (continued)

## Histopathology Observations – Animal Cross Reference

Removal Reason: All of those selected

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| SPLEEN; (continued) | | | | | | | | |
| Within Normal Limits (continued) | 5486 | | | 5576 | 5476 | | | 5566 |
| | 5487 | | | 5577 | 5477 | | | 5567 |
| | 5488 | | | 5578 | 5478 | | | 5568 |
| | 5489 | | | 5579 | 5479 | | | 5569 |
| | 5490 | | | 5580 | 5480 | | | 5570 |
| | 5491 | | | 5581 | 5481 | | | 5571 |
| | 5492 | | | 5582 | 5482 | | | 5572 |
| | 5493 | | | 5583 | 5483 | | | 5573 |
| STOMACH; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 5484 | | | 5574 | 5474 | | | 5564 |
| | 5485 | | | 5575 | 5475 | | | 5565 |
| | 5486 | | | 5576 | 5476 | | | 5566 |
| | 5487 | | | 5577 | 5477 | | | 5567 |
| | 5488 | | | 5578 | 5478 | | | 5568 |
| | 5489 | | | 5579 | 5479 | | | 5569 |
| | 5490 | | | 5580 | 5480 | | | 5570 |
| | 5491 | | | 5581 | 5481 | | | 5571 |
| | 5492 | | | 5582 | 5482 | | | 5572 |
| | 5493 | | | 5583 | 5483 | | | 5573 |
| TESTES; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (-) | (-) | (-) | (-) |
| Within Normal Limits | 5484 | | | 5574 | | | | |
| | 5485 | | | 5575 | | | | |
| | 5486 | | | 5576 | | | | |
| | 5487 | | | 5577 | | | | |
| | 5488 | | | 5578 | | | | |
| | 5489 | | | 5579 | | | | |
| | 5490 | | | 5580 | | | | |
| | 5491 | | | 5581 | | | | |
| | 5492 | | | 5582 | | | | |
| | 5493 | | | | | | | |
| seminiferous tubule; Cyst | | | | 5583 | | | | |

# APPENDIX O

## Attachment 4 (continued)

## Histopathology Observations – Animal Cross Reference

Removal Reason: All of those selected

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| TESTES; (continued) | | | | | | | | |
| spermatid; Degeneration; minimal | | | | 5583 | | | | |
| THYMUS; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 5464 | | | 5574 | 5474 | | | 5564 |
| | 5485 | | | 5575 | 5475 | | | 5565 |
| | 5486 | | | 5576 | 5476 | | | 5566 |
| | 5487 | | | 5577 | 5477 | | | 5567 |
| | 5488 | | | 5578 | 5478 | | | 5568 |
| | 5489 | | | 5579 | 5479 | | | 5569 |
| | 5490 | | | 5580 | 5480 | | | 5570 |
| | 5491 | | | 5581 | 5481 | | | 5571 |
| | 5492 | | | 5582 | 5482 | | | 5572 |
| | 5493 | | | 5583 | 5483 | | | 5573 |
| THYROID GLANDS; | | | | | | | | |
| Examined | (10) | (10) | (10) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 5485 | 5514 | 5545 | 5580 | 5474 | | | 5564 |
| | 5486 | 5515 | 5548 | | 5476 | | | 5566 |
| | 5488 | 5517 | | | 5478 | | | 5568 |
| | 5489 | 5519 | | | 5479 | | | 5569 |
| | 5490 | 5520 | | | 5480 | | | 5570 |
| | 5492 | 5522 | | | 5481 | | | 5571 |
| | 5493 | 5523 | | | 5482 | | | |
| Cyst; ultimobranchial | 5484 | 5516 | | 5576 | 5475 | | | 5567 |
| | 5491 | 5518 | | | 5477 | | | 5572 |
| | | 5521 | | | | | | 5573 |
| Ectopic Thymus | 5487 | | | | 5483 | | | |
| Hypertrophy; follicular; minimal | 5487 | | 5547 | 5579 | | | | 5565 |
| | | | 5549 | | | | | |
| | | | 5550 | | | | | |
| | | | 5552 | | | | | |
| | | | 5553 | | | | | |

# APPENDIX O

## Attachment 4 (continued)

## Histopathology Observations – Animal Cross Reference

Removal Reason: All of those selected

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| THYROID GLANDS; (continued) | | | | | | | | |
| mild | | | 5544<br>5546<br>5551 | 5574<br>5575<br>5576<br>5577<br>5578<br>5581<br>5582<br>5583 | | | | |
| TRACHEA; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 5484<br>5485<br>5486<br>5487<br>5488<br>5489<br>5490<br>5491<br>5492<br>5493 | | | 5574<br>5575<br>5576<br>5577<br>5578<br>5579<br>5580<br>5581<br>5582<br>5583 | 5474<br>5475<br>5476<br>5477<br>5478<br>5479<br>5480<br>5481<br>5482<br>5483 | | | 5564<br>5565<br>5566<br>5567<br>5568<br>5569<br>5570<br>5571<br>5572<br>5573 |
| URINARY BLADDER; | | | | | | | | |
| Examined | (10) | (0) | (0) | (10) | (10) | (0) | (0) | (10) |
| Within Normal Limits | 5484<br>5485<br>5486<br>5487<br>5488<br>5489<br>5490<br>5491<br>5492<br>5493 | | | 5574<br>5575<br>5576<br>5577<br>5578<br>5579<br>5580<br>5581<br>5582<br>5583 | 5474<br>5475<br>5476<br>5477<br>5478<br>5479<br>5480<br>5481<br>5482<br>5483 | | | 5564<br>5565<br>5566<br>5567<br>5568<br>5570<br>5571<br>5572<br>5573 |
| Inflammation; chronic; focal; | | | | | | | | |
| minimal | | | | | | | | 5569 |

# APPENDIX O

## Attachment 4 (continued)

## Histopathology Observations – Animal Cross Reference

Removal Reason: All of those selected

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg | 0mg/kg | 50mg/kg | 250mg/kg | 500mg/kg |
| UTERUS; | | | | | | | | |
| Examined | (-) | (-) | (-) | (-) | (10) | (0) | (0) | (10) |
| Within Normal Limits | | | | | 5474 | | | 5564 |
| | | | | | 5475 | | | 5565 |
| | | | | | 5476 | | | 5566 |
| | | | | | 5477 | | | 5567 |
| | | | | | 5478 | | | 5568 |
| | | | | | 5479 | | | 5569 |
| | | | | | 5481 | | | 5570 |
| | | | | | 5482 | | | 5571 |
| | | | | | 5483 | | | 5572 |
| | | | | | | | | 5573 |
| Inflammation; acute; diffuse; mild | | | | | 5480 | | | |

# APPENDIX O

## Attachment 5

## Individual Gross Pathology Data

SEX: MALE

| GROUP | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| REMOVAL REASON | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R |
| ANIMAL NUMBER | 544 | 548 | 546 | 547 | 548 | 548 | 549 | 540 | 541 | 542 | 543 | 545 | 551 | 556 | 557 | 558 | 559 | 560 | 561 | 562 | 563 | 564 | 565 | 567 | 568 | 569 | 570 | 571 | 573 | 574 | 575 | 576 | 577 | 578 | 579 | 580 | 581 | 582 | 583 |
| ADRENAL GLANDS; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | + | N | N | N | N | N | N | N | + | N | N | + | N | N | N | + | N | N | N | N | N | N | N | N | N |
| Discoloration; dark | . | . | . | . | . | . | . | . | . | . | . | . | . | . | P | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| Discoloration; red; unilateral; single | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | P | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| Enlarged | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | P | . | . | . | P | . | . | . | . | . | . | . | . | . |
| BONE MARROW, STERNUM; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| BRAIN; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| EPIDIDYMIDES; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| HEART; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| INTESTINE, CECUM; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| INTESTINE, COLON; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | + | + | N | N | N | N | + | N | N | N | N | N |
| Dilation | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | P | P | . | . | . | . | P | . | . | . | . | . |
| INTESTINE, DUODENUM; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| INTESTINE, ILEUM; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| INTESTINE, JEJUNUM; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| KIDNEYS; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | + | N | N |
| Discoloration; yellow; unilateral | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | P | . | . |
| LIVER; | N | N | N | N | N | N | N | N | N | N | N | N | N | + | N | N | N | N | N | N | N | + | N | N | + | N | N | N | N | N | + | + | + | + | + | + | N | + |
| Discoloration; mottled | . | . | . | . | . | . | . | . | . | . | . | . | . | P | . | . | . | . | . | . | . | P | . | . | P | . | . | . | . | . | P | P | P | P | P | P | . | . |
| Enlarged | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | P |

Group: 1 - 0mg/kg, 2 - 50mg/kg, 3 - 250mg/kg, 4 - 500mg/kg

R - Scheduled Necropsy - Isoflurane/Exsanguination
N - N.V.L.
. - Not Recorded
+ - Tissue Observation Present
X - Not Examined
# - duplicate
P - present - no grade or classification

# APPENDIX O

## Attachment 5 (continued)

## Individual Gross Pathology Data

SEX: MALE

| GROUP | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| REMOVAL REASON | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R |
| ANIMAL NUMBER | 5448 | 5446 | 5447 | 5448 | 5448 | 5449 | 5440 | 5491 | 5492 | 5493 | 5495 | 5511 | 5556 | 5557 | 5558 | 5559 | 5560 | 5561 | 5562 | 5563 | 5564 | 5565 | 5567 | 5568 | 5569 | 5570 | 5571 | 5572 | 5573 | 5574 | 5575 | 5576 | 5577 | 5578 | 5579 | 5580 | 5583 |
| LUNGS; | N | N | N | N | N | N | N | N | N | N | N | N | + | N | N | N | N | N | N | N | N | + | + | N | N | N | N | N | + | N | + | + | + | N | N | N | N |
| Discoloration; dark; multiple | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | P | P | . | . | . | . | . | . | . | P | . | P | . | . | . | . |
| Discoloration; focal | . | . | . | . | . | . | . | . | . | . | . | . | P | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | P | . | . | . | . | . | . | . | . |
| Hemorrhage; red; single | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | P | . | . | . | . |
| LYMPH NODE, MEDIASTINAL; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| LYMPH NODE, MESENTERIC; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| NERVE, SCIATIC; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| PROSTATE GLAND; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| SEMINAL VESICLES; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | + | N | N | N | N | N | N | N | N | N | N | N | + | N | N | N | N | N | + |
| Small | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | P | . | . | . | . | . | . | . | . | . | . | . | P | . | . | . | . | . | . |
| Enlarged | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | P |
| SPINAL CORD; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| SPLEEN; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | + | N | N | N | N | N | N | N | N | N | N | N | N |
| Enlarged | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | P | . | . | . | . | . | . | . | . | . | . | . | . |
| STOMACH; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| TESTES; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | + | N | N |
| Discoloration; hemorrhagic; unilateral | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | P | . | . |
| THYMUS; | + | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | + | + | N | N | N | + | + | N | N | + | N | + | N | + | + | N | + |
| Discoloration; dark; multiple | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | P | . | . |
| Discoloration; few | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | P | . | . | . | . | . | . | . | . | . | . | . |
| Discoloration; red; multiple | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | P | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| Discoloration; red; unilateral; multifocal | P | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |

Group: 1 - 0mg/kg, 2 - 50mg/kg, 3 - 250mg/kg, 4 - 500mg/kg

R - Scheduled Necropsy - Isoflurane/Exsanguination
N - N.V.L.
. - Not Recorded
+ - Tissue Observation Present
X - Not Examined
# - duplicate
P - present - no grade or classification

# APPENDIX O

## Attachment 5 (continued)

## Individual Gross Pathology Data

SEX: MALE

| GROUP | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| REMOVAL REASON | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R |
| ANIMAL NUMBER | 548 | 548 | 548 | 548 | 548 | 548 | 549 | 549 | 549 | 549 | 551 | 551 | 551 | 551 | 551 | 551 | 552 | 552 | 552 | 552 | 554 | 554 | 554 | 554 | 554 | 554 | 554 | 554 | 557 | 557 | 557 | 557 | 557 | 557 | 558 | 558 | 558 |
| | 45 | 46 | 47 | 48 | 49 | 50 | 01 | 02 | 03 | 04 | 45 | 56 | 67 | 78 | 89 | 90 | 12 | 23 | 34 | 45 | 56 | 67 | 78 | 89 | 01 | 12 | 23 | 34 | 45 | 56 | 67 | 76 | 89 | 90 | 12 | 23 | 34 |
| THYMUS; (Continued) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Small | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | P | P | . | . | . | . | P | . | . | P | . | P | . | P | . |
| THYROID GLANDS; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| TRACHEA; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| URINARY BLADDER; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N |

Group: 1 - 0mg/kg, 2 - 50mg/kg, 3 - 250mg/kg, 4 - 500mg/kg

R - Scheduled Necropsy - Isoflurane/Exsanguination
N - N.V.L.
. - Not Recorded
+ - Tissue Observation Present
X - Not Examined
# - duplicate
P - present - no grade or classification

# APPENDIX O

## Attachment 5 (continued)

## Individual Gross Pathology Data

SEX: FEMALE

| GROUP | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| REMOVAL REASON | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R |
| ANIMAL NUMBER | 54 | 54 | 54 | 54 | 54 | 54 | 54 | 54 | 54 | 54 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 |
| | 74 | 75 | 76 | 77 | 78 | 79 | 80 | 81 | 82 | 83 | 05 | 06 | 07 | 08 | 09 | 01 | 12 | 23 | 13 | 34 | 35 | 56 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | 51 | 52 | 53 |
| ADRENAL GLANDS; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | + | N | N | + | N | N |
| Enlarged | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | P | . | . | P | . | . |
| BONE MARROW, STERNUM; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| BRAIN; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| HEART; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| INTESTINE, CECUM; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| INTESTINE, COLON; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | + | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | + | N | N | N | N |
| Dilation | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | P | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | P | . | . | . | . |
| INTESTINE, DUODENUM; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| INTESTINE, ILEUM; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| INTESTINE, JEJUNUM; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| KIDNEYS; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| LIVER; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | + | + | N | N | N | N | + | + | + | + | + | + | + |
| Discoloration | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | P | . | . | . | . | . | . | P | . | . | . | P |
| Discoloration; mottled | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | P | . | . | . | . | . | . | . | . | . | P | . | . |
| Enlarged | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | P | . | . | . | . | P | P | . | P | . | . | P |
| LUNGS; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | + | N | N | N | N | N | N | N |

Group: 1 - 0mg/kg, 2 - 50mg/kg, 3 - 250mg/kg, 4 - 500mg/kg

R - Scheduled Necropsy - Isoflurane/Exsanguination
N - N.V.I.
. - Not Recorded
+ - Tissue Observation Present
X - Not Examined
# - duplicate
P - present - no grade or classification

# APPENDIX O

## Attachment 5 (continued)

## Individual Gross Pathology Data

SEX: FEMALE

| GROUP | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| REMOVAL REASON | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R |
| ANIMAL NUMBER | 5447 | 5447 | 5447 | 5447 | 5447 | 5447 | 5448 | 5448 | 5448 | 5448 | 5550 | 5550 | 5550 | 5550 | 5550 | 5551 | 5551 | 5551 | 5553 | 5553 | 5553 | 5553 | 5553 | 5554 | 5554 | 5554 | 5554 | 5556 | 5556 | 5556 | 5556 | 5556 | 5557 | 5557 | 5557 | 5557 | 5557 |
| | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 8 | 7 | 8 | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 |
| LYMPH NODE, MEDIASTINAL; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| LYMPH NODE, MESENTERIC; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| NERVE, SCIATIC; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| OVARIES; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | + | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Enlarged | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | P | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| SPINAL CORD; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| SPLEEN; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | + | N | N | N | N | N | N | N | N | N | N | N | + | N | N | N | N | N | N | N | N | N | N | N | N |
| Discoloration; dark | . | . | . | . | . | . | . | . | . | . | . | . | . | . | P | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| Enlarged | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | P | . | . | . | . | . | . | . | . | . | . | . | . |
| STOMACH; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| THYMUS; | N | N | N | N | N | N | N | N | N | N | + | N | N | N | N | N | N | + | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Discoloration | . | . | . | . | . | . | . | . | . | . | P | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| Discoloration; red; multifocal | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | P | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| Enlarged | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | # | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| THYROID GLANDS; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| TRACHEA; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| URINARY BLADDER; | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N | N | N | N |
| UTERUS; | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |

Group: 1 - 0mg/kg, 2 - 50mg/kg, 3 - 250mg/kg, 4 - 500mg/kg

R - Scheduled Necropsy - Isoflurane/Exsanguination
N - N.V.L.
. - Not Recorded
+ - Tissue Observation Present
X - Not Examined
# - duplicate
P - present - no grade or classification

# APPENDIX O

## Attachment 6

## Individual Histopathology Data

SEX: MALE

| GROUP | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| REMOVAL REASON | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R |
| ANIMAL NUMBER | 548 | 548 | 548 | 548 | 548 | 549 | 549 | 549 | 549 | 549 | 551 | 551 | 551 | 551 | 551 | 551 | 552 | 552 | 552 | 552 | 554 | 554 | 554 | 554 | 554 | 554 | 555 | 555 | 555 | 555 | 557 | 557 | 557 | 557 | 557 | 557 | 558 | 558 | 558 | 558 |
| ADRENAL GLANDS; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N | N |
| BONE MARROW, STERNUM; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N | N |
| BRAIN; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N | N |
| EPIDIDYMIDES; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N | + |
| spermatid; Immature | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | 1 |
| HEART; | N | + | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | + | N | N | N | N | N |
| Inflammation; chronic; focal | . | 1 | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | 1 | . | . | . | . | . |
| INTESTINE, CECUM; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N | N |
| INTESTINE, COLON; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N | N |
| INTESTINE, DUODENUM; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N | N |
| INTESTINE, ILEUM; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N | N |
| INTESTINE, JEJUNUM; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N | N |
| KIDNEYS; | N | N | + | + | N | + | N | N | + | + | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | + | + | N | N | + | + | + |
| Hyperplasia; tubular; focal | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | 3 | . | . |
| Infarction; focal | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | 3 | . | . |
| Inflammation; chronic; focal | . | . | . | . | . | 1 | . | . | 1 | 1 | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | 1 | . |
| Basophilia; tubular; focal | . | . | 1 | 1 | . | 2 | . | . | 1 | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | 1 | 1 | . | . | 2 | 1 | 1 |
| LIVER; | + | + | N | + | + | + | + | + | + | + | + | + | + | + | + | N | + | + | + | N | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Inflammation; chronic; multifocal | 1 | 1 | . | 1 | 1 | 1 | 1 | 1 | 2 | 1 | 2 | 1 | 1 | 1 | . | 1 | 1 | 1 | . | 1 | . | 1 | 1 | 1 | 1 | 1 | 1 | . | 1 | 1 | . | . | . | . | . | . | . | . | . | 1 |
| Hyperplasia, Bile Duct, Assoc W Pps | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | 3 | 1 | 3 | 2 | 1 | . | 2 | 2 | 1 | . |
| Protoporphyrinosis | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | 3 | 1 | 3 | 1 | 1 | 1 | 3 | 2 | 1 | . |

# APPENDIX O

## Attachment 6

## Individual Histopathology Data

SEX: MALE

| GROUP | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| REMOVAL REASON | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R |
| ANIMAL NUMBER | 5 4 8 4 | 5 4 8 5 | 5 4 8 6 | 5 4 8 7 | 5 4 8 8 | 5 4 8 9 | 5 4 9 0 | 5 4 9 1 | 5 4 9 2 | 5 4 9 3 | 5 5 1 4 | 5 5 1 5 | 5 5 1 6 | 5 5 1 7 | 5 5 1 8 | 5 5 1 9 | 5 5 2 0 | 5 5 2 1 | 5 5 2 2 | 5 5 2 3 | 5 5 2 4 | 5 5 4 5 | 5 5 4 6 | 5 5 4 7 | 5 5 4 8 | 5 5 5 9 | 5 5 5 0 | 5 5 5 1 | 5 5 5 2 | 5 5 5 3 | 5 5 5 4 | 5 5 5 5 | 5 5 7 6 | 5 5 7 7 | 5 5 7 8 | 5 5 7 9 | 5 5 8 0 | 5 5 8 1 | 5 5 8 2 | 5 5 8 3 |
| LIVER; (Continued) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| centrilobular; Hypertrophy | . | . | . | . | . | . | . | . | . | . | . | . | . | 1 | . | . | . | . | . | . | 1 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | . | . | 2 | . | 2 | 2 | 2 | 2 | . | 1 | 1 | 1 |
| centrilobular; Vacuolation; hepatocellular | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | 2 | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| periportal; Inflammation; chronic | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | 2 | 1 | 2 | 2 | 1 | 1 | 2 | 2 | 1 | . |
| periportal; Vacuolation; hepatocellular | 1 | . | . | . | . | . | . | . | 2 | . | . | . | . | . | . | . | . | . | . | . | . | . | 1 | . | . | 2 | . | . | . | . | . | . | . | 2 | . | 2 | 2 | . | . | . |
| LUNGS; | + | N | + | N | + | N | + | + | + | + | + | + | + | N | N | N | + | N | N | N | + | N | + | + | + | + | + | + | + | N | + | N | + | + | + | + | + | N | + | + |
| Hemorrhage; focal | 1 | . | . | . | . | . | . | . | . | 1 | . | . | . | . | . | . | . | . | . | . | . | . | 1 | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | 1 |
| Inflammation; acute; focal | 1 | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| Inflammation; chronic; focal | . | . | . | . | . | . | . | . | . | 1 | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | 1 | . | . | . | . | . | . |
| Inflammation; chronic; multifocal | . | . | . | . | . | . | . | 1 | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| Histocytosis | . | . | 1 | . | 1 | . | 1 | . | 1 | . | 1 | 1 | 1 | . | . | . | 1 | . | . | . | 2 | . | 2 | 2 | 1 | 1 | 2 | 1 | 1 | . | 1 | . | 1 | 1 | 1 | 1 | 1 | . | 1 | 1 |
| lymphoid tissue; Hyperplasia | . | . | . | . | . | . | . | . | . | . | 2 | . | . | . | . | . | . | . | . | . | . | . | . | . | . | 2 | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| LYMPH NODE, MEDIASTINAL; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N | N |
| LYMPH NODE, MESENTERIC; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N | N |
| NERVE, SCIATIC; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N | N |
| PROSTATE GLAND; | N | N | N | N | N | + | + | N | N | N | + | + | + | N | + | + | N | + | + | N | N | + | + | N | + | N | + | N | + | N | + | + | N | N | + | + | N | + | + | + |
| Inflammation; chronic | . | . | . | . | . | 2 | 3 | . | . | . | 1 | 2 | 1 | . | . | 2 | . | 1 | 3 | . | . | 1 | 1 | . | 1 | . | 1 | . | 1 | . | 2 | 2 | . | . | 2 | 2 | . | 1 | 2 | 2 |
| Inflammation; chronic-active | . | . | . | . | . | . | . | . | . | . | . | . | . | . | 4 | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| Necrosis; single cell | . | . | . | . | . | . | 1 | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | 1 |
| SEMINAL VESICLES; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N | + |
| Atrophy; unilateral | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | 2 |
| SPINAL CORD; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N | N |

Group: 1 - 0mg/kg. 2 - 50mg/kg, 3 - 250mg/kg, 4 - 500mg/kg

R - Scheduled Necropsy - Isoflurane/Exsanguination
N - N.V.L
. - Not Recorded
+ - Tissue Observation Present
X - Not Examined
1 - minimal
2 - mild
3 - moderate
4 - marked
# - duplicate
P - present - no grade or classification

# APPENDIX O

## Attachment 6

## Individual Histopathology Data

SEX: MALE

| GROUP | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| REMOVAL REASON | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R |
| ANIMAL NUMBER | 54 | 54 | 54 | 54 | 54 | 54 | 54 | 54 | 54 | 54 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 |
| | 84 | 88 | 88 | 88 | 88 | 89 | 89 | 89 | 89 | 89 | 11 | 11 | 11 | 11 | 11 | 12 | 12 | 12 | 12 | 44 | 44 | 44 | 44 | 44 | 45 | 55 | 55 | 55 | 57 | 57 | 57 | 57 | 57 | 58 | 58 | 58 | 58 |
| | 45 | 56 | 67 | 69 | 90 | 01 | 12 | 23 | 34 | 45 | 56 | 67 | 69 | 90 | 01 | 12 | 23 | 34 | 45 | 56 | 67 | 78 | 89 | 90 | 01 | 12 | 23 | 34 | 45 | 56 | 67 | 78 | 89 | 01 | 12 | 23 | 23 |
| SPLEEN; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N |
| STOMACH; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N |
| TESTES; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | + |
| seminiferous tubule; Cyst | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | P |
| spermatid; Degeneration | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | 1 |
| THYMUS; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N |
| THYROID GLANDS; | + | N | N | + | N | N | N | + | N | N | N | N | + | N | + | N | N | + | N | N | + | N | + | + | N | + | + | + | + | + | + | + | + | N | + | + | + |
| Cyst; ultimobranchial | P | . | . | . | . | . | . | P | . | . | . | . | P | . | P | . | . | P | . | . | . | . | . | . | . | . | . | . | . | . | P | . | . | . | . | . | . |
| Ectopic Thymus | . | . | . | P | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| Hypertrophy; follicular | . | . | . | 1 | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | 2 | . | 2 | 1 | . | 1 | 1 | 2 | 1 | 1 | 2 | 2 | 2 | 2 | 1 | . | 2 | 2 | 2 |
| TRACHEA; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N |
| URINARY BLADDER; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N |

Group: 1 - 0mg/kg. 2 - 50mg/kg, 3 - 250mg/kg, 4 - 500mg/kg

R - Scheduled Necropsy - Isoflurane/Exsanguination
N - N.V.L
. - Not Recorded
+ - Tissue Observation Present
X - Not Examined
1 - minimal
2 - mild
3 - moderate
4 - marked
# - duplicate
P - present - no grade or classification

# APPENDIX O

## Attachment 6

## Individual Histopathology Data

SEX: FEMALE

| GROUP | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| REMOVAL REASON | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R |
| ANIMAL NUMBER | 5447 | 5447 | 5447 | 5447 | 5447 | 5447 | 5448 | 5448 | 5448 | 5448 | 5550 | 5550 | 5550 | 5550 | 5550 | 5551 | 5551 | 5551 | 5553 | 5553 | 5553 | 5553 | 5554 | 5554 | 5554 | 5554 | 5554 | 5556 | 5556 | 5556 | 5556 | 5556 | 5557 | 5557 | 5557 | 5557 | 5557 |
| | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 |

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ADRENAL GLANDS; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N | N |
| BONE MARROW, STERNUM; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N | N |
| BRAIN; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N | N |
| HEART; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N | + |
| atrium; endocardium; Hyperplasia | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | 2 |
| INTESTINE, CECUM; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N | N |
| INTESTINE, COLON; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N | N |
| INTESTINE, DUODENUM; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N | N |
| INTESTINE, ILEUM; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N | N |
| INTESTINE, JEJUNUM; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N | N |
| KIDNEYS; | + | + | N | + | + | + | + | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | + | N | N | N | N | N | N | + | N | + |
| Inflammation; chronic; focal | 1 | 1 | . | . | . | 1 | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | 1 | . | . | . | . | . | . | . | . | . |
| Basophilia; tubular; focal | . | . | . | 1 | 1 | . | 1 | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | 1 | . | 1 |
| LIVER; | + | + | N | + | + | + | + | + | N | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Inflammation; chronic; multifocal | . | 1 | . | 1 | 1 | 2 | 1 | 1 | . | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | . | 1 | 1 | . | . | . | 2 | 2 | . | . | . | . | 1 | . | . | 1 | 1 | 1 |
| centrilobular; Hypertrophy | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | 1 | 2 | 1 | . | . | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| periportal; Vacuolation; hepatocellular | 2 | 1 | . | 1 | 1 | 2 | . | . | . | . | . | . | 1 | . | 1 | 1 | 1 | . | 2 | 1 | 1 | 3 | 2 | . | . | . | 3 | 2 | 3 | 3 | 2 | 3 | 2 | 3 | 2 | 2 | 2 |
| LUNGS; | N | + | N | N | + | + | N | N | N | N | + | + | + | N | + | + | N | N | N | N | N | N | + | N | + | N | N | N | + | N | N | + | N | + | + | N | + | + | N |
| Hemorrhage; focal | . | . | . | . | . | . | . | . | . | . | . | . | . | . | 1 | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| Inflammation; acute; focal | . | . | . | . | . | . | . | . | . | . | 1 | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| Inflammation; chronic; focal | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | 1 | . | . | . | . | . | . | . | . | . | . | . | . | . | . |

Group: 1 - 0mg/kg. 2 - 50mg/kg, 3 - 250mg/kg, 4 - 500mg/kg

R - Scheduled Necropsy - Isoflurane/Exsanguination
N - N.V.L
. - Not Recorded
+ - Tissue Observation Present
X - Not Examined
1 - minimal
2 - mild
3 - moderate
4 - marked
# - duplicate
P - present - no grade or classification

# APPENDIX O

## Attachment 6

## Individual Histopathology Data

SEX: FEMALE

| GROUP | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| REMOVAL REASON | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R |
| ANIMAL NUMBER | 5447 | 5447 | 5447 | 5447 | 5447 | 5447 | 5448 | 5448 | 5448 | 5448 | 5450 | 5550 | 5550 | 5550 | 5550 | 5550 | 5551 | 5551 | 5553 | 5553 | 5553 | 5553 | 5554 | 5554 | 5554 | 5554 | 5554 | 5556 | 5556 | 5556 | 5556 | 5556 | 5557 | 5557 | 5557 | 5557 | 5557 |
| | 45 | 46 | 67 | 78 | 90 | 01 | 12 | 23 | 35 | 56 | 67 | 78 | 89 | 90 | 01 | 12 | 23 | 34 | 45 | 56 | 78 | 89 | 01 | 12 | 23 | 34 | 45 | 58 | 67 | 78 | 89 | 90 | 01 | 12 | 23 |

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| LUNGS; (Continued) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Histocytosis | . | 1 | . | . | 1 | 1 | . | . | . | . | 1 | 1 | . | . | . | 1 | . | . | . | . | . | 1 | . | 2 | . | . | . | . | . | 1 | . | 1 | 1 | . | 1 | 1 | . |
| lymphoid tissue; Hyperplasia | . | . | . | . | . | . | . | . | . | . | . | 2 | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | 2 | . | . | . | . | . | . | . | . | . |
| LYMPH NODE, MEDIASTINAL; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N | N |
| LYMPH NODE, MESENTERIC; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N | N |
| NERVE, SCIATIC; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N | N |
| OVARIES; | N | N | N | N | + | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | + | N | N | N | N | N | N | N | N |
| corpus luteum; Cyst | . | . | . | . | P | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | P | . | . | . | . | . | . | . | . |
| SPINAL CORD; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N | N |
| SPLEEN; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N | N |
| STOMACH; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N | N |
| THYMUS; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N | N |
| THYROID GLANDS; | N | + | N | + | N | N | N | N | N | + | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | + | N | + | N | N | N | N | + | + |
| Cyst; ultimobranchial | . | P | . | P | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | P | . | . | . | . | P | P |
| Ectopic Thymus | . | . | . | . | . | . | . | . | . | P | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| Hypertrophy; follicular | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | 1 | . | . | . | . | . | . | . | . |
| TRACHEA; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N | N |
| URINARY BLADDER; | N | N | N | N | N | N | N | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | + | N | N | N | N |
| Inflammation; chronic; focal | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | 1 | . | . | . | . |

Group: 1 - 0mg/kg. 2 - 50mg/kg, 3 - 250mg/kg, 4 - 500mg/kg

R - Scheduled Necropsy - Isoflurane/Exsanguination
N - N.V.L
. - Not Recorded
+ - Tissue Observation Present
X - Not Examined
1 - minimal
2 - mild
3 - moderate
4 - marked
# - duplicate
P - present - no grade or classification

# APPENDIX O

## Attachment 6

## Individual Histopathology Data

SEX: FEMALE

| GROUP | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| REMOVAL REASON | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R |
| ANIMAL NUMBER | 5447 | 5447 | 5447 | 5447 | 5447 | 5447 | 5448 | 5448 | 5448 | 5448 | 5550 | 5550 | 5550 | 5550 | 5550 | 5551 | 5551 | 5551 | 5551 | 5553 | 5553 | 5553 | 5553 | 5554 | 5554 | 5554 | 5554 | 5554 | 5556 | 5556 | 5556 | 5556 | 5556 | 5557 | 5557 | 5557 | 5557 | 5557 |
| | 4567 | 4567 | 4567 | 4567 | 4567 | 4567 | 4567 | 4567 | 4567 | 4567 | 5678 | 5678 | 5678 | 5678 | 5678 | 9012 | 9012 | 9012 | 9012 | 3456 | 3456 | 3456 | 3456 | 3901 | 3901 | 3901 | 3901 | 3901 | 4623 | 4623 | 4623 | 4623 | 4623 | 6789 | 6789 | 6789 | 6789 | 6789 |
| UTERUS; | N | N | N | N | N | N | + | N | N | N | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | N | N | N | N | N | N | N | N | N | N |
| Inflammation; acute; diffuse | . | . | . | . | . | . | 2 | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |

Group: 1 - 0mg/kg. 2 - 50mg/kg, 3 - 250mg/kg, 4 - 500mg/kg

R - Scheduled Necropsy - Isoflurane/Exsanguination
N - N.V.L
. - Not Recorded
+ - Tissue Observation Present
X - Not Examined
1 - minimal
2 - mild
3 - moderate
4 - marked
# - duplicate
P - present - no grade or classification

# Appendix P: Individual Organ Weights (grams) and Organ Weights to Body Weight Ratios – Male Rats

| Group Sex | Animal Number | Bodywt g | Adrenal g | Adrenal/ BW | Brain g | Brain/ BW | Epidid-ymides g | Epididy-mides/BW | Heart g |
|---|---|---|---|---|---|---|---|---|---|
| 1m | 5484 | 462.8 | 0.0715 | 0.0002 | 1.852 | 0.004 | 1.363 | 0.003 | 1.281 |
| | 5485 | 399.4 | 0.0662 | 0.0002 | 1.940 | 0.005 | 1.213 | 0.003 | 1.238 |
| | 5486 | 414.2 | 0.0567 | 0.0001 | 2.023 | 0.005 | 1.254 | 0.003 | 1.285 |
| | 5487 | 447.0 | 0.0428 | 0.0001 | 1.965 | 0.004 | 1.164 | 0.003 | 1.485 |
| | 5488 | 442.3 | 0.0771 | 0.0002 | 2.036 | 0.005 | 1.114 | 0.003 | 1.389 |
| | 5489 | 440.4 | 0.0551 | 0.0001 | 2.102 | 0.005 | 1.142 | 0.003 | 1.613 |
| | 5490 | 451.0 | 0.0515 | 0.0001 | 1.957 | 0.004 | 1.300 | 0.003 | 1.406 |
| | 5491 | 447.6 | 0.0570 | 0.0001 | 1.968 | 0.004 | 1.061 | 0.002 | 1.309 |
| | 5492 | 390.1 | 0.0631 | 0.0002 | 1.993 | 0.005 | 1.218 | 0.003 | 1.276 |
| | 5493 | 413.5 | 0.0525 | 0.0001 | 2.110 | 0.005 | 1.331 | 0.003 | 1.352 |
| | Mean | 430.83 | 0.05935 | 0.00014 | 1.9946 | 0.0046 | 1.2160 | 0.0029 | 1.3634 |
| | S.D. | 24.54 | 0.01020 | 0.00005 | 0.0772 | 0.0005 | 0.0977 | 0.0003 | 0.1150 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix P: Individual Organ Weights (grams) and Organ Weights to Body Weight Ratios – Male Rats

| Group Sex | Animal Number | Heart/ BW | Kidney g | Kidney/ BW | Liver g | Liver/ BW | Prostate g | Prostate/ BW |
|---|---|---|---|---|---|---|---|---|
| 1m | 5484 | 0.003 | 2.858 | 0.006 | 12.957 | 0.028 | 0.933 | 0.002 |
| | 5485 | 0.003 | 2.667 | 0.007 | 10.967 | 0.027 | 0.738 | 0.002 |
| | 5486 | 0.003 | 2.914 | 0.007 | 12.843 | 0.031 | 0.878 | 0.002 |
| | 5487 | 0.003 | 3.131 | 0.007 | 13.893 | 0.031 | 0.678 | 0.002 |
| | 5488 | 0.003 | 2.744 | 0.006 | 12.977 | 0.029 | 0.977 | 0.002 |
| | 5489 | 0.004 | 2.959 | 0.007 | 13.085 | 0.030 | 0.893 | 0.002 |
| | 5490 | 0.003 | 2.855 | 0.006 | 12.555 | 0.028 | 0.929 | 0.002 |
| | 5491 | 0.003 | 2.765 | 0.006 | 13.273 | 0.030 | 0.780 | 0.002 |
| | 5492 | 0.003 | 2.669 | 0.007 | 10.948 | 0.028 | 0.846 | 0.002 |
| | 5493 | 0.003 | 2.855 | 0.007 | 10.604 | 0.026 | 0.770 | 0.002 |
| | Mean | 0.0031 | 2.8417 | 0.0066 | 12.4102 | 0.0288 | 0.8422 | 0.0020 |
| | S.D. | 0.0003 | 0.1411 | 0.0005 | 1.1407 | 0.0017 | 0.0970 | 0.0000 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix P: Individual Organ Weights (grams) and Organ Weights to Body Weight Ratios – Male Rats

| Group Sex | Animal Number | Bodywt g | Testes g | Testes/ BW | Thymus g | Thymus/ BW | Seminal Vessicle g | Seminal Vess/BW | Spleen g | Spleen/ BW |
|---|---|---|---|---|---|---|---|---|---|---|
| 1m | 5484 | 462.8 | 3.682 | 0.008 | 0.507 | 0.001 | 1.688 | 0.004 | 0.758 | 0.002 |
| | 5485 | 399.4 | 3.520 | 0.009 | 0.387 | 0.001 | 1.548 | 0.004 | 0.811 | 0.002 |
| | 5486 | 414.2 | 3.888 | 0.009 | 0.474 | 0.001 | 2.153 | 0.005 | 0.689 | 0.002 |
| | 5487 | 447.0 | 3.316 | 0.007 | 0.380 | 0.001 | 1.484 | 0.003 | 0.713 | 0.002 |
| | 5488 | 442.3 | 3.290 | 0.007 | 0.365 | 0.001 | 2.023 | 0.005 | 0.645 | 0.001 |
| | 5489 | 440.4 | 3.227 | 0.007 | 0.599 | 0.001 | 2.053 | 0.005 | 0.902 | 0.002 |
| | 5490 | 451.0 | 3.396 | 0.008 | 0.501 | 0.001 | 2.132 | 0.005 | 0.849 | 0.002 |
| | 5491 | 447.6 | 3.279 | 0.007 | 0.344 | 0.001 | 1.620 | 0.004 | 0.677 | 0.002 |
| | 5492 | 390.1 | 3.536 | 0.009 | 0.227 | 0.001 | 1.939 | 0.005 | 0.667 | 0.002 |
| | 5493 | 413.5 | 3.484 | 0.008 | 0.481 | 0.001 | 1.903 | 0.005 | 0.565 | 0.001 |
| | Mean | 430.83 | 3.4618 | 0.0079 | 0.4265 | 0.0010 | 1.8543 | 0.0045 | 0.7276 | 0.0018 |
| | S.D. | 24.54 | 0.2063 | 0.0009 | 0.1060 | 0.0000 | 0.2488 | 0.0007 | 0.1023 | 0.0004 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix P: Individual Organ Weights (grams) and Organ Weights to Body Weight Ratios – Male Rats

| Group Sex | Animal Number | Bodywt g | Adrenal g | Adrenal/ BW | Brain g | Brain/ BW | Epidid- ymides g | Epididy- mides/BW | Heart g |
|---|---|---|---|---|---|---|---|---|---|
| 2m | 5514 | 355.8 | 0.0579 | 0.0002 | 1.948 | 0.005 | 1.139 | 0.003 | 1.070 |
| | 5515 | 428.6 | 0.0519 | 0.0001 | 1.960 | 0.005 | 1.101 | 0.003 | 1.269 |
| | 5516 | 434.9 | 0.0604 | 0.0001 | 1.910 | 0.004 | 1.144 | 0.003 | 1.386 |
| | 5517 | 454.2 | 0.0521 | 0.0001 | 1.963 | 0.004 | 1.174 | 0.003 | 1.249 |
| | 5518 | 441.7 | 0.0559 | 0.0001 | 2.149 | 0.005 | 1.243 | 0.003 | 1.306 |
| | 5519 | 434.6 | 0.0515 | 0.0001 | 2.017 | 0.005 | 1.367 | 0.003 | 1.353 |
| | 5520 | 393.1 | 0.0612 | 0.0002 | 1.913 | 0.005 | 1.325 | 0.003 | 1.295 |
| | 5521 | 430.7 | 0.0455 | 0.0001 | 1.941 | 0.005 | 1.135 | 0.003 | 1.341 |
| | 5522 | 453.2 | 0.0550 | 0.0001 | 2.060 | 0.005 | 1.214 | 0.003 | 1.325 |
| | 5523 | 388.3 | 0.0568 | 0.0001 | 1.884 | 0.005 | 1.087 | 0.003 | 1.275 |
| | Mean | 421.51 | 0.05482 | 0.00012 | 1.9745 | 0.0048 | 1.1929 | 0.0030 | 1.2869 |
| | S.D. | 31.96 | 0.00472 | 0.00004 | 0.0802 | 0.0004 | 0.0939 | 0.0000 | 0.0869 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Nominal Dose: Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix P: Individual Organ Weights (grams) and Organ Weights to Body Weight Ratios – Male Rats

| Group Sex | Animal Number | Heart/ BW | Kidney g | Kidney/ BW | Liver g | Liver/ BW | Prostate g | Prostate/ BW |
|---|---|---|---|---|---|---|---|---|
| 2m | 5514 | 0.003 | 2.548 | 0.007 | 10.365 | 0.029 | 0.677 | 0.002 |
| | 5515 | 0.003 | 2.964 | 0.007 | 13.454 | 0.031 | 0.870 | 0.002 |
| | 5516 | 0.003 | 3.255 | 0.007 | 12.725 | 0.029 | 0.930 | 0.002 |
| | 5517 | 0.003 | 3.029 | 0.007 | 14.087 | 0.031 | 0.720 | 0.002 |
| | 5518 | 0.003 | 2.525 | 0.006 | 14.305 | 0.032 | 1.197 | 0.003 |
| | 5519 | 0.003 | 2.839 | 0.007 | 13.589 | 0.031 | 0.822 | 0.002 |
| | 5520 | 0.003 | 2.987 | 0.008 | 11.656 | 0.030 | 0.755 | 0.002 |
| | 5521 | 0.003 | 2.830 | 0.007 | 13.114 | 0.030 | 0.731 | 0.002 |
| | 5522 | 0.003 | 3.012 | 0.007 | 12.976 | 0.029 | 0.998 | 0.002 |
| | 5523 | 0.003 | 2.583 | 0.007 | 11.558 | 0.030 | 0.671 | 0.002 |
| | Mean | 0.0030 | 2.8572 | 0.0070 | 12.7829 | 0.0302 | 0.8371 | 0.0021 |
| | S.D. | 0.0000 | 0.2409 | 0.0005 | 1.2421 | 0.0010 | 0.1668 | 0.0003 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

## Appendix P: Individual Organ Weights (grams) and Organ Weights to Body Weight Ratios – Male Rats

| Group Sex | Animal Number | Bodywt g | Testes g | Testes/ BW | Thymus g | Thymus/ BW | Seminal Vessicle g | Seminal Vess/BW | Spleen g | Spleen/ BW |
|---|---|---|---|---|---|---|---|---|---|---|
| 2m | 5514 | 355.8 | 3.600 | 0.010 | 0.250 | 0.001 | 1.246 | 0.004 | 0.602 | 0.002 |
| | 5515 | 428.6 | 3.236 | 0.008 | 0.458 | 0.001 | 1.163 | 0.003 | 0.795 | 0.002 |
| | 5516 | 434.9 | 3.393 | 0.008 | 0.493 | 0.001 | 1.916 | 0.004 | 0.653 | 0.002 |
| | 5517 | 454.2 | 3.516 | 0.008 | 0.421 | 0.001 | 1.541 | 0.003 | 0.714 | 0.002 |
| | 5518 | 441.7 | 3.336 | 0.008 | 0.536 | 0.001 | 2.163 | 0.005 | 0.833 | 0.002 |
| | 5519 | 434.6 | 3.832 | 0.009 | 0.434 | 0.001 | 1.641 | 0.004 | 0.657 | 0.002 |
| | 5520 | 393.1 | 3.712 | 0.009 | 0.352 | 0.001 | 1.807 | 0.005 | 0.772 | 0.002 |
| | 5521 | 430.7 | 3.145 | 0.007 | 0.406 | 0.001 | 1.388 | 0.003 | 0.718 | 0.002 |
| | 5522 | 453.2 | 3.831 | 0.008 | 0.449 | 0.001 | 1.777 | 0.004 | 0.750 | 0.002 |
| | 5523 | 388.3 | 3.499 | 0.009 | 0.457 | 0.001 | 0.997 | 0.003 | 0.752 | 0.002 |
| | Mean | 421.51 | 3.5100 | 0.0084 | 0.4256 | 0.0010 | 1.5639 | 0.0038 | 0.7246 | 0.0020 |
| | S.D. | 31.96 | 0.2376 | 0.0008 | 0.0789 | 0.0000 | 0.3664 | 0.0008 | 0.0709 | 0.0000 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix P: Individual Organ Weights (grams) and Organ Weights to Body Weight Ratios – Male Rats

| Group Sex | Animal Number | Bodywt g | Adrenal g | Adrenal/ BW | Brain g | Brain/ BW | Epidid- ymides g | Epididy- mides/BW | Heart g |
|---|---|---|---|---|---|---|---|---|---|
| 3m | 5544 | 422.5 | 0.0536 | 0.0001 | 2.064 | 0.005 | 1.065 | 0.003 | 1.199 |
| | 5545 | 434.0 | 0.0512 | 0.0001 | 1.873 | 0.004 | 1.145 | 0.003 | 1.273 |
| | 5546 | 455.5 | 0.0595 | 0.0001 | 2.133 | 0.005 | 1.139 | 0.003 | 1.617 |
| | 5547 | 440.1 | 0.0507 | 0.0001 | 1.985 | 0.005 | 1.160 | 0.003 | 1.320 |
| | 5548 | 426.8 | 0.0513 | 0.0001 | 1.973 | 0.005 | 1.210 | 0.003 | 1.312 |
| | 5549 | 449.5 | 0.0741 | 0.0002 | 1.957 | 0.004 | 1.149 | 0.003 | 1.455 |
| | 5550 | 389.1 | 0.0525 | 0.0001 | 2.079 | 0.005 | 1.110 | 0.003 | 1.164 |
| | 5551 | 400.4 | 0.0513 | 0.0001 | 2.017 | 0.005 | 1.226 | 0.003 | 1.237 |
| | 5552 | 392.8 | 0.0515 | 0.0001 | 2.036 | 0.005 | 1.238 | 0.003 | 1.300 |
| | 5553 | 391.5 | 0.0644 | 0.0002 | 1.788 | 0.005 | 1.211 | 0.003 | 1.555 |
| | Mean | 420.22 | 0.05601 | 0.00012 | 1.9905 | 0.0048 | 1.1653 | 0.0030 | 1.3432 |
| | S.D. | 25.11 | 0.00777 | 0.00004 | 0.1014 | 0.0004 | 0.0553 | 0.0000 | 0.1509 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix P: Individual Organ Weights (grams) and Organ Weights to Body Weight Ratios – Male Rats

| Group Sex | Animal Number | Heart/ BW | Kidney g | Kidney/ BW | Liver g | Liver/ BW | Prostate g | Prostate/ BW |
|---|---|---|---|---|---|---|---|---|
| 3m | 5544 | 0.003 | 2.715 | 0.006 | 16.292 | 0.039 | 0.623 | 0.001 |
| | 5545 | 0.003 | 2.962 | 0.007 | 14.580 | 0.034 | 0.745 | 0.002 |
| | 5546 | 0.004 | 3.846 | 0.008 | 17.128 | 0.038 | 0.969 | 0.002 |
| | 5547 | 0.003 | 2.850 | 0.006 | 14.315 | 0.033 | 0.647 | 0.001 |
| | 5548 | 0.003 | 2.988 | 0.007 | 16.006 | 0.038 | 0.815 | 0.002 |
| | 5549 | 0.003 | 3.435 | 0.008 | 17.794 | 0.040 | 0.816 | 0.002 |
| | 5550 | 0.003 | 2.768 | 0.007 | 12.499 | 0.032 | 1.118 | 0.003 |
| | 5551 | 0.003 | 3.173 | 0.008 | 14.403 | 0.036 | 0.827 | 0.002 |
| | 5552 | 0.003 | 2.954 | 0.008 | 12.887 | 0.033 | 0.929 | 0.002 |
| | 5553 | 0.004 | 2.608 | 0.007 | 12.215 | 0.031 | 0.755 | 0.002 |
| | Mean | 0.0032 | 3.0299 | 0.0072 | 14.8119 | 0.0354 | 0.8244 | 0.0019 |
| | S.D. | 0.0004 | 0.3713 | 0.0008 | 1.9477 | 0.0032 | 0.1496 | 0.0006 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix P: Individual Organ Weights (grams) and Organ Weights to Body Weight Ratios – Male Rats

| Group Sex | Animal Number | Bodywt g | Testes g | Testes/ BW | Thymus g | Thymus/ BW | Seminal Vessicle g | Seminal Vess/BW | Spleen g | Spleen/ BW |
|---|---|---|---|---|---|---|---|---|---|---|
| 3m | 5544 | 422.5 | 2.943 | 0.007 | 0.350 | 0.001 | 1.581 | 0.004 | 0.737 | 0.002 |
| | 5545 | 434.0 | 3.194 | 0.007 | 0.390 | 0.001 | 1.833 | 0.004 | 0.645 | 0.001 |
| | 5546 | 455.5 | 3.430 | 0.008 | 0.328 | 0.001 | 1.755 | 0.004 | 0.672 | 0.001 |
| | 5547 | 440.1 | 3.654 | 0.008 | 0.290 | 0.001 | 1.564 | 0.004 | 0.801 | 0.002 |
| | 5548 | 426.8 | 3.415 | 0.008 | 0.212 | 0.000 | 2.346 | 0.005 | 0.780 | 0.002 |
| | 5549 | 449.5 | 3.079 | 0.007 | 0.483 | 0.001 | 1.788 | 0.004 | 0.792 | 0.002 |
| | 5550 | 389.1 | 3.237 | 0.008 | 0.453 | 0.001 | 1.437 | 0.004 | 0.899 | 0.002 |
| | 5551 | 400.4 | 3.442 | 0.009 | 0.414 | 0.001 | 1.509 | 0.004 | 0.702 | 0.002 |
| | 5552 | 392.8 | 3.726 | 0.009 | 0.330 | 0.001 | 1.327 | 0.003 | 0.682 | 0.002 |
| | 5553 | 391.5 | 3.523 | 0.009 | 0.259 | 0.001 | 1.908 | 0.005 | 0.611 | 0.002 |
| | Mean | 420.22 | 3.3643 | 0.0080 | 0.3509 | 0.0009 | 1.7048 | 0.0041 | 0.7321 | 0.0018 |
| | S.D. | 25.11 | 0.2488 | 0.0008 | 0.0855 | 0.0003 | 0.2918 | 0.0006 | 0.0868 | 0.0004 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix P: Individual Organ Weights (grams) and Organ Weights to Body Weight Ratios – Male Rats

| Group Sex | Animal Number | Bodywt g | Adrenal g | Adrenal/ BW | Brain g | Brain/ BW | Epidid- ymides g | Epididy- mides/BW | Heart g |
|---|---|---|---|---|---|---|---|---|---|
| 4m | 5574 | 375.5 | 0.0454 | 0.0001 | 1.929 | 0.005 | 1.089 | 0.003 | 1.117 |
| | 5575 | 363.7 | 0.0355 | 0.0001 | 1.989 | 0.005 | 1.146 | 0.003 | 1.114 |
| | 5576 | 372.9 | 0.0497 | 0.0001 | 1.954 | 0.005 | 1.000 | 0.003 | 1.095 |
| | 5577 | 429.3 | 0.0508 | 0.0001 | 2.018 | 0.005 | 1.098 | 0.003 | 1.310 |
| | 5578 | 433.5 | 0.0431 | 0.0001 | 1.914 | 0.004 | 1.190 | 0.003 | 1.278 |
| | 5579 | 394.2 | 0.0401 | 0.0001 | 1.978 | 0.005 | 1.262 | 0.003 | 1.218 |
| | 5580 | 386.0 | 0.0380 | 0.0001 | 1.897 | 0.005 | 1.075 | 0.003 | 1.201 |
| | 5581 | 427.7 | 0.0567 | 0.0001 | 2.115 | 0.005 | 1.162 | 0.003 | 1.506 |
| | 5582 | 401.7 | 0.0480 | 0.0001 | 1.816 | 0.005 | 1.142 | 0.003 | 1.369 |
| | 5583 | 427.5 | 0.0441 | 0.0001 | 2.070 | 0.005 | 1.060 | 0.002 | 1.327 |
| | Mean | 401.20 | 0.04514 | 0.00010 | 1.9680 | 0.0049 | 1.1224 | 0.0029 | 1.2535 |
| | S.D. | 26.61 | 0.00641 | 0.00000 | 0.0868 | 0.0003 | 0.0741 | 0.0003 | 0.1306 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix P: Individual Organ Weights (grams) and Organ Weights to Body Weight Ratios – Male Rats

Day: 30 relative to Start Date

| Group Sex | Animal Number | Heart/ BW | Kidney g | Kidney/ BW | Liver g | Liver/ BW | Prostate g | Prostate/ BW |
|---|---|---|---|---|---|---|---|---|
| 4m | 5574 | 0.003 | 2.679 | 0.007 | 14.561 | 0.039 | 0.586 | 0.002 |
| | 5575 | 0.003 | 2.625 | 0.007 | 13.737 | 0.038 | 0.675 | 0.002 |
| | 5576 | 0.003 | 2.573 | 0.007 | 17.196 | 0.046 | 0.448 | 0.001 |
| | 5577 | 0.003 | 2.959 | 0.007 | 16.132 | 0.038 | 0.772 | 0.002 |
| | 5578 | 0.003 | 3.065 | 0.007 | 17.890 | 0.041 | 1.022 | 0.002 |
| | 5579 | 0.003 | 2.983 | 0.008 | 16.386 | 0.042 | 0.774 | 0.002 |
| | 5580 | 0.003 | 2.589 | 0.007 | 16.714 | 0.043 | 0.677 | 0.002 |
| | 5581 | 0.004 | 2.856 | 0.007 | 15.913 | 0.037 | 0.915 | 0.002 |
| | 5582 | 0.003 | 3.174 | 0.008 | 17.978 | 0.045 | 0.598 | 0.001 |
| | 5583 | 0.003 | 3.005 | 0.007 | 15.814 | 0.037 | 0.880 | 0.002 |
| | Mean | 0.0031 | 2.8508 | 0.0072 | 16.2321 | 0.0406 | 0.7347 | 0.0018 |
| | S.D. | 0.0003 | 0.2185 | 0.0004 | 1.3452 | 0.0033 | 0.1729 | 0.0004 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix P: Individual Organ Weights (grams) and Organ Weights to Body Weight Ratios – Male Rats

| Group Sex | Animal Number | Bodywt g | Testes g | Testes/ BW | Thymus g | Thymus/ BW | Seminal Vessicle g | Seminal Vess/BW | Spleen g | Spleen/ BW |
|---|---|---|---|---|---|---|---|---|---|---|
| 4m | 5574 | 375.5 | 2.943 | 0.008 | 0.294 | 0.001 | 1.743 | 0.005 | 0.484 | 0.001 |
| | 5575 | 363.7 | 3.013 | 0.008 | 0.322 | 0.001 | 1.519 | 0.004 | 0.615 | 0.002 |
| | 5576 | 372.9 | 2.715 | 0.007 | 0.171 | 0.000 | 0.810 | 0.002 | 0.608 | 0.002 |
| | 5577 | 429.3 | 3.108 | 0.007 | 0.343 | 0.001 | 1.683 | 0.004 | 0.785 | 0.002 |
| | 5578 | 433.5 | 3.147 | 0.007 | 0.354 | 0.001 | 2.141 | 0.005 | 0.666 | 0.002 |
| | 5579 | 394.2 | 3.451 | 0.009 | 0.284 | 0.001 | 2.104 | 0.005 | 0.571 | 0.001 |
| | 5580 | 386.0 | 3.097 | 0.008 | 0.201 | 0.001 | 1.330 | 0.003 | 0.563 | 0.001 |
| | 5581 | 427.7 | 3.304 | 0.008 | 0.361 | 0.001 | 1.811 | 0.004 | 0.826 | 0.002 |
| | 5582 | 401.7 | 3.246 | 0.008 | 0.410 | 0.001 | 1.392 | 0.003 | 0.709 | 0.002 |
| | 5583 | 427.5 | 2.527 | 0.006 | 0.195 | 0.000 | 2.603 | 0.006 | 0.554 | 0.001 |
| | Mean | 401.20 | 3.0551 | 0.0076 | 0.2935 | 0.0008 | 1.7136 | 0.0041 | 0.6381 | 0.0016 |
| | S.D. | 26.61 | 0.2743 | 0.0008 | 0.0806 | 0.0004 | 0.4991 | 0.0012 | 0.1081 | 0.0005 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix Q: Individual Organ Weights (grams) and Organ to Body Weight Ratios – Toxicity Group Female Rats

| Group Sex | Animal Number | Bodywt g | Adrenal g | Adrenal/ BW | Brain g | Brain/ BW | Heart g | Heart/ BW | Kidney g | Kidney/ BW | Liver g |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1f | 5474 | 235.7 | 0.0654 | 0.0003 | 1.807 | 0.008 | 0.791 | 0.003 | 1.741 | 0.007 | 6.788 |
| | 5475 | 276.4 | 0.0622 | 0.0002 | 1.965 | 0.007 | 0.895 | 0.003 | 1.642 | 0.006 | 7.010 |
| | 5476 | 238.1 | 0.0726 | 0.0003 | 1.890 | 0.008 | 0.807 | 0.003 | 1.617 | 0.007 | 6.826 |
| | 5477 | 244.2 | 0.0731 | 0.0003 | 2.015 | 0.008 | 0.822 | 0.003 | 1.625 | 0.007 | 6.552 |
| | 5478 | 295.3 | 0.1095 | 0.0004 | 1.979 | 0.007 | 1.064 | 0.004 | 1.932 | 0.007 | 9.334 |
| | 5479 | 287.7 | 0.0740 | 0.0003 | 1.958 | 0.007 | 0.913 | 0.003 | 1.788 | 0.006 | 8.240 |
| | 5480 | 267.7 | 0.0732 | 0.0003 | 1.859 | 0.007 | 0.883 | 0.003 | 1.720 | 0.006 | 8.345 |
| | 5481 | 276.9 | 0.0592 | 0.0002 | 2.258 | 0.008 | 1.019 | 0.004 | 2.172 | 0.008 | 8.374 |
| | 5482 | 247.1 | 0.0500 | 0.0002 | 1.763 | 0.007 | 0.819 | 0.003 | 1.821 | 0.007 | 6.832 |
| | 5483 | 226.5 | 0.0691 | 0.0003 | 1.823 | 0.008 | 0.800 | 0.004 | 1.580 | 0.007 | 6.527 |
| | Mean | 259.56 | 0.07083 | 0.00028 | 1.9317 | 0.0075 | 0.8813 | 0.0033 | 1.7638 | 0.0068 | 7.4828 |
| | S.D. | 24.11 | 0.01562 | 0.00006 | 0.1415 | 0.0005 | 0.0950 | 0.0005 | 0.1797 | 0.0006 | 0.9933 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix Q: Individual Organ Weights (grams) and Organ to Body Weight Ratios – Toxicity Group Female Rats

| Group Sex | Animal Number | Liver/ BW | Ovaries g | Ovaries/ BW | Spleen g | Spleen/ BW | Thymus g | Thymus/ BW | Uterus g | Uterus/ BW |
|---|---|---|---|---|---|---|---|---|---|---|
| 1f | 5474 | 0.029 | 0.1135 | 0.0005 | 0.571 | 0.002 | 0.331 | 0.001 | 0.344 | 0.0015 |
| | 5475 | 0.025 | 0.1381 | 0.0005 | 0.443 | 0.002 | 0.443 | 0.002 | 0.522 | 0.0019 |
| | 5476 | 0.029 | 0.1103 | 0.0005 | 0.524 | 0.002 | 0.410 | 0.002 | 0.575 | 0.0024 |
| | 5477 | 0.027 | 0.1160 | 0.0005 | 0.442 | 0.002 | 0.346 | 0.001 | 0.498 | 0.0020 |
| | 5478 | 0.032 | 0.1728 | 0.0006 | 0.789 | 0.003 | 0.744 | 0.003 | 0.407 | 0.0014 |
| | 5479 | 0.029 | 0.1401 | 0.0005 | 0.594 | 0.002 | 0.375 | 0.001 | 0.440 | 0.0015 |
| | 5480 | 0.031 | 0.1414 | 0.0005 | 0.426 | 0.002 | 0.386 | 0.001 | 0.465 | 0.0017 |
| | 5481 | 0.030 | 0.1717 | 0.0006 | 0.615 | 0.002 | 0.347 | 0.001 | 1.006 | 0.0036 |
| | 5482 | 0.028 | 0.1102 | 0.0004 | 0.491 | 0.002 | 0.394 | 0.002 | 0.403 | 0.0016 |
| | 5483 | 0.029 | 0.1178 | 0.0005 | 0.464 | 0.002 | 0.387 | 0.002 | 0.446 | 0.0020 |
| | Mean | 0.0289 | 0.13319 | 0.00051 | 0.5359 | 0.0021 | 0.4163 | 0.0016 | 0.5106 | 0.00196 |
| | S.D. | 0.0020 | 0.02395 | 0.00006 | 0.1114 | 0.0003 | 0.1198 | 0.0007 | 0.1859 | 0.00065 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix Q: Individual Organ Weights (grams) and Organ to Body Weight Ratios – Toxicity Group Female Rats

| Group Sex | Animal Number | Bodywt g | Adrenal g | Adrenal/ BW | Brain g | Brain/ BW | Heart g | Heart/ BW | Kidney g | Kidney/ BW | Liver g |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2f | 5505 | 242.3 | 0.0655 | 0.0003 | 1.841 | 0.008 | 0.866 | 0.004 | 1.852 | 0.008 | 7.744 |
| | 5506 | 238.1 | 0.0522 | 0.0002 | 1.854 | 0.008 | 0.722 | 0.003 | 1.538 | 0.006 | 6.250 |
| | 5507 | 261.0 | 0.0688 | 0.0003 | 1.970 | 0.008 | 0.877 | 0.003 | 1.972 | 0.008 | 7.598 |
| | 5508 | 269.6 | 0.0720 | 0.0003 | 1.938 | 0.007 | 0.861 | 0.003 | 1.780 | 0.007 | 7.737 |
| | 5509 | 276.5 | 0.0850 | 0.0003 | 1.972 | 0.007 | 0.926 | 0.003 | 1.857 | 0.007 | 8.073 |
| | 5510 | 267.3 | 0.0654 | 0.0002 | 1.967 | 0.007 | 0.957 | 0.004 | 1.831 | 0.007 | 8.321 |
| | 5511 | 237.2 | 0.0687 | 0.0003 | 1.849 | 0.008 | 0.786 | 0.003 | 1.704 | 0.007 | 6.628 |
| | 5512 | 224.6 | 0.0665 | 0.0003 | 1.919 | 0.009 | 0.746 | 0.003 | 1.586 | 0.007 | 6.795 |
| | 5513 | 290.3 | 0.0671 | 0.0002 | 1.956 | 0.007 | 0.893 | 0.003 | 1.975 | 0.007 | 7.739 |
| | Mean | 256.32 | 0.06791 | 0.00027 | 1.9184 | 0.0077 | 0.8482 | 0.0032 | 1.7883 | 0.0071 | 7.4317 |
| | S.D. | 21.74 | 0.00845 | 0.00005 | 0.0555 | 0.0007 | 0.0802 | 0.0004 | 0.1541 | 0.0006 | 0.7038 |
| | N | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix Q: Individual Organ Weights (grams) and Organ to Body Weight Ratios – Toxicity Group Female Rats

| Group Sex | Animal Number | Liver/ BW | Ovaries g | Ovaries/ BW | Spleen g | Spleen/ BW | Thymus g | Thymus/ BW | Uterus g | Uterus/ BW |
|---|---|---|---|---|---|---|---|---|---|---|
| 2f | 5505 | 0.032 | 0.1312 | 0.0005 | 0.548 | 0.002 | 0.316 | 0.001 | 0.482 | 0.0020 |
| | 5506 | 0.026 | 0.1323 | 0.0006 | 0.501 | 0.002 | 0.328 | 0.001 | 0.463 | 0.0019 |
| | 5507 | 0.029 | 0.1467 | 0.0006 | 0.544 | 0.002 | 0.419 | 0.002 | 0.534 | 0.0020 |
| | 5508 | 0.029 | 0.1110 | 0.0004 | 0.610 | 0.002 | 0.483 | 0.002 | 0.440 | 0.0016 |
| | 5509 | 0.029 | 0.1622 | 0.0006 | 0.625 | 0.002 | 0.378 | 0.001 | 0.556 | 0.0020 |
| | 5510 | 0.031 | 0.1523 | 0.0006 | 0.701 | 0.003 | 0.466 | 0.002 | 0.630 | 0.0024 |
| | 5511 | 0.028 | 0.1064 | 0.0004 | 0.534 | 0.002 | 0.507 | 0.002 | 0.461 | 0.0019 |
| | 5512 | 0.030 | 0.1109 | 0.0005 | 0.458 | 0.002 | 0.296 | 0.001 | 0.508 | 0.0023 |
| | 5513 | 0.027 | 0.1606 | 0.0006 | 0.651 | 0.002 | 0.769 | 0.003 | 0.537 | 0.0018 |
| | Mean | 0.0290 | 0.13484 | 0.00053 | 0.5747 | 0.0021 | 0.4402 | 0.0017 | 0.5123 | 0.00199 |
| | S.D. | 0.0019 | 0.02187 | 0.00009 | 0.0774 | 0.0003 | 0.1450 | 0.0007 | 0.0592 | 0.00024 |
| | N | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix Q: Individual Organ Weights (grams) and Organ to Body Weight Ratios – Toxicity Group Female Rats

| Group Sex | Animal Number | Bodywt g | Adrenal g | Adrenal/ BW | Brain g | Brain/ BW | Heart g | Heart/ BW | Kidney g | Kidney/ BW | Liver g |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 3f | 5534 | 252.4 | 0.0673 | 0.0003 | 1.791 | 0.007 | 0.829 | 0.003 | 1.741 | 0.007 | 9.397 |
| | 5535 | 225.7 | 0.0599 | 0.0003 | 1.877 | 0.008 | 0.753 | 0.003 | 1.467 | 0.006 | 7.823 |
| | 5536 | 268.7 | 0.0696 | 0.0003 | 1.922 | 0.007 | 0.914 | 0.003 | 2.103 | 0.008 | 9.426 |
| | 5537 | 256.7 | 0.0711 | 0.0003 | 1.929 | 0.008 | 0.817 | 0.003 | 1.753 | 0.007 | 9.014 |
| | 5538 | 237.6 | 0.0756 | 0.0003 | 1.817 | 0.008 | 0.802 | 0.003 | 1.555 | 0.007 | 7.756 |
| | 5539 | 279.8 | 0.0863 | 0.0003 | 1.983 | 0.007 | 0.934 | 0.003 | 2.020 | 0.007 | 11.458 |
| | 5540 | 259.6 | 0.0813 | 0.0003 | 1.947 | 0.008 | 0.907 | 0.003 | 1.786 | 0.007 | 8.994 |
| | 5541 | 258.6 | 0.0683 | 0.0003 | 1.923 | 0.007 | 0.898 | 0.003 | 1.830 | 0.007 | 9.700 |
| | 5542 | 264.0 | 0.0689 | 0.0003 | 1.950 | 0.007 | 0.859 | 0.003 | 1.838 | 0.007 | 9.524 |
| | 5543 | 276.8 | 0.0680 | 0.0002 | 1.901 | 0.007 | 0.925 | 0.003 | 1.924 | 0.007 | 9.753 |
| | Mean | 257.99 | 0.07163 | 0.00029 | 1.9040 | 0.0074 | 0.8638 | 0.0030 | 1.8017 | 0.0070 | 9.2845 |
| | S.D. | 16.58 | 0.00758 | 0.00003 | 0.0602 | 0.0005 | 0.0612 | 0.0000 | 0.1928 | 0.0005 | 1.0454 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix Q: Individual Organ Weights (grams) and Organ to Body Weight Ratios – Toxicity Group Female Rats

| Group Sex | Animal Number | Liver/ BW | Ovaries g | Ovaries/ BW | Spleen g | Spleen/ BW | Thymus g | Thymus/ BW | Uterus g | Uterus/ BW |
|---|---|---|---|---|---|---|---|---|---|---|
| 3f | 5534 | 0.037 | 0.1610 | 0.0006 | 0.607 | 0.002 | 0.283 | 0.001 | 0.707 | 0.0028 |
| | 5535 | 0.035 | 0.1204 | 0.0005 | 0.396 | 0.002 | 0.377 | 0.002 | 0.350 | 0.0016 |
| | 5536 | 0.035 | 0.1312 | 0.0005 | 0.505 | 0.002 | 0.335 | 0.001 | 0.454 | 0.0017 |
| | 5537 | 0.035 | 0.1480 | 0.0006 | 0.499 | 0.002 | 0.375 | 0.001 | 0.447 | 0.0017 |
| | 5538 | 0.033 | 0.1062 | 0.0004 | 0.433 | 0.002 | 0.354 | 0.001 | 1.545 | 0.0065 |
| | 5539 | 0.041 | 0.1244 | 0.0004 | 0.595 | 0.002 | 0.387 | 0.001 | 0.560 | 0.0020 |
| | 5540 | 0.035 | 0.1265 | 0.0005 | 0.537 | 0.002 | 0.303 | 0.001 | 0.445 | 0.0017 |
| | 5541 | 0.038 | 0.1181 | 0.0005 | 0.445 | 0.002 | 0.435 | 0.002 | 1.460 | 0.0056 |
| | 5542 | 0.036 | 0.1191 | 0.0005 | 0.684 | 0.003 | 0.502 | 0.002 | 0.861 | 0.0033 |
| | 5543 | 0.035 | 0.1328 | 0.0005 | 0.623 | 0.002 | 0.362 | 0.001 | 0.419 | 0.0015 |
| | Mean | 0.0360 | 0.12877 | 0.00050 | 0.5324 | 0.0021 | 0.3713 | 0.0013 | 0.7248 | 0.00284 |
| | S.D. | 0.0022 | 0.01578 | 0.00007 | 0.0935 | 0.0003 | 0.0629 | 0.0005 | 0.4374 | 0.00180 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix Q: Individual Organ Weights (grams) and Organ to Body Weight Ratios – Toxicity Group Female Rats

| Group Sex | Animal Number | Bodywt g | Adrenal g | Adrenal/ BW | Brain g | Brain/ BW | Heart g | Heart/ BW | Kidney g | Kidney/ BW | Liver g |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 4f | 5564 | 236.1 | 0.0564 | 0.0002 | 1.887 | 0.008 | 0.801 | 0.003 | 1.672 | 0.007 | 11.346 |
| | 5565 | 230.3 | 0.0601 | 0.0003 | 1.942 | 0.008 | 0.878 | 0.004 | 1.576 | 0.007 | 9.987 |
| | 5566 | 271.7 | 0.0720 | 0.0003 | 2.014 | 0.007 | 0.976 | 0.004 | 1.841 | 0.007 | 12.340 |
| | 5567 | 235.5 | 0.0541 | 0.0002 | 1.811 | 0.008 | 0.802 | 0.003 | 1.707 | 0.007 | 11.455 |
| | 5568 | 255.2 | 0.0796 | 0.0003 | 1.823 | 0.007 | 0.837 | 0.003 | 1.736 | 0.007 | 12.349 |
| | 5569 | 259.2 | 0.0715 | 0.0003 | 1.958 | 0.008 | 0.927 | 0.004 | 1.914 | 0.007 | 14.416 |
| | 5570 | 233.2 | 0.0505 | 0.0002 | 1.914 | 0.008 | 0.808 | 0.003 | 1.600 | 0.007 | 9.768 |
| | 5571 | 292.4 | 0.0809 | 0.0003 | 1.976 | 0.007 | 0.930 | 0.003 | 1.905 | 0.007 | 13.315 |
| | 5572 | 280.1 | 0.0741 | 0.0003 | 1.875 | 0.007 | 0.917 | 0.003 | 1.758 | 0.006 | 12.958 |
| | 5573 | 251.0 | 0.0834 | 0.0003 | 1.963 | 0.008 | 0.864 | 0.003 | 1.696 | 0.007 | 12.750 |
| | Mean | 254.47 | 0.06826 | 0.00027 | 1.9163 | 0.0076 | 0.8740 | 0.0033 | 1.7405 | 0.0069 | 12.0684 |
| | S.D. | 21.50 | 0.01202 | 0.00005 | 0.0667 | 0.0005 | 0.0620 | 0.0005 | 0.1165 | 0.0003 | 1.4528 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix Q: Individual Organ Weights (grams) and Organ to Body Weight Ratios – Toxicity Group Female Rats

| Group Sex | Animal Number | Liver/ BW | Ovaries g | Ovaries/ BW | Spleen g | Spleen/ BW | Thymus g | Thymus/ BW | Uterus g | Uterus/ BW |
|---|---|---|---|---|---|---|---|---|---|---|
| 4f | 5564 | 0.048 | 0.1299 | 0.0006 | 0.508 | 0.002 | 0.263 | 0.001 | 0.443 | 0.0019 |
| | 5565 | 0.043 | 0.1130 | 0.0005 | 0.549 | 0.002 | 0.357 | 0.002 | 0.440 | 0.0019 |
| | 5566 | 0.045 | 0.1627 | 0.0006 | 0.712 | 0.003 | 0.302 | 0.001 | 0.801 | 0.0029 |
| | 5567 | 0.049 | 0.1205 | 0.0005 | 0.421 | 0.002 | 0.312 | 0.001 | 0.403 | 0.0017 |
| | 5568 | 0.048 | 0.1305 | 0.0005 | 0.373 | 0.001 | 0.321 | 0.001 | 0.484 | 0.0019 |
| | 5569 | 0.056 | 0.1427 | 0.0006 | 0.496 | 0.002 | 0.332 | 0.001 | 0.488 | 0.0019 |
| | 5570 | 0.042 | 0.1520 | 0.0007 | 0.441 | 0.002 | 0.285 | 0.001 | 0.425 | 0.0018 |
| | 5571 | 0.046 | 0.1629 | 0.0006 | 0.730 | 0.002 | 0.452 | 0.002 | 0.359 | 0.0012 |
| | 5572 | 0.046 | 0.1758 | 0.0006 | 0.628 | 0.002 | 0.413 | 0.001 | 0.618 | 0.0022 |
| | 5573 | 0.051 | 0.1344 | 0.0005 | 0.388 | 0.002 | 0.293 | 0.001 | 0.492 | 0.0020 |
| | Mean | 0.0474 | 0.14244 | 0.00057 | 0.5246 | 0.0020 | 0.3330 | 0.0012 | 0.4953 | 0.00194 |
| | S.D. | 0.0041 | 0.02040 | 0.00007 | 0.1287 | 0.0005 | 0.0591 | 0.0004 | 0.1276 | 0.00042 |
| | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix R: Individual Reproductive Parameters – Reproductive Group Female Rats

| Group | Sex | Animal | Day Number | Live Males | Dead Males | Live Females | Dead Females | Live Pups | Male PP4 | Dead Male Pups PP4 | Live Females | Female Pups PP4 | Litter Wt. 0 g | Litter Wt. Term g |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | f | 5494 | 56 | 8 | 0 | 6 | 1 | | 8 | 0 | 6 | 0 | 86.9 | 132.2 |
| | | 5495 | 56 | 9 | 0 | 7 | 0 | | 9 | 0 | 7 | 0 | 106.4 | 180.6 |
| | | 5496 | 56 | 9 | 0 | 9 | 0 | | 9 | 0 | 9 | 0 | 119.7 | 197.7 |
| | | 5497 | 56 | 8 | 1 | 9 | 0 | | 8 | 0 | 9 | 0 | 101.6 | 174.8 |
| | | 5498 | 56 | 10 | 0 | 6 | 0 | | 11 | 0 | 5 | 0 | 115.6 | 178.1 |
| | | 5499 | 56 | 4 | 1 | 5 | 2 | | 3 | 1 | 5 | 0 | 83.5 | 119.4 |
| | | 5500 | 56 | 10 | 0 | 6 | 0 | | 10 | 0 | 6 | 0 | 108.8 | 167.2 |
| | | 5502 | 56 | 9 | 0 | 6 | 0 | | 9 | 0 | 6 | 0 | 105.4 | 165.4 |
| | | 5503 | 56 | 8 | 0 | 8 | 0 | | 8 | 0 | 8 | 0 | 106.8 | 161.5 |
| 2 | f | 5504 | 56 | 6 | 0 | 9 | 0 | | 6 | 0 | 9 | 0 | 100.9 | 170.3 |
| | | 5524 | 56 | 8 | 0 | 8 | 0 | | 8 | 0 | 8 | 0 | 97.8 | 168.3 |
| | | 5525 | 56 | 8 | 0 | 8 | 0 | | 8 | 0 | 8 | 0 | 103.2 | 154.0 |
| | | 5526 | 56 | 6 | 0 | 6 | 0 | | 6 | 0 | 6 | 0 | 85.2 | 130.6 |
| | | 5527 | 56 | 10 | 0 | 7 | 0 | | 10 | 0 | 6 | 1 | 112.5 | 169.7 |
| | | 5528 | 56 | 11 | 0 | 6 | 0 | | 11 | 0 | 6 | 0 | 115.5 | 169.5 |
| | | 5529 | 56 | 5 | 1 | 7 | 0 | | 5 | 0 | 7 | 0 | 83.1 | 144.2 |
| | | 5531 | 56 | 11 | 0 | 5 | 0 | | 11 | 0 | 4 | 1 | 104.9 | 167.6 |
| | | 5532 | 56 | 8 | 0 | 10 | 0 | | 8 | 0 | 10 | 0 | 119.4 | 193.1 |
| 3 | f | 5554 | 56 | 12 | 0 | 3 | 0 | | 12 | 0 | 3 | 0 | 98.3 | 159.7 |
| | | 5555 | 56 | 5 | 0 | 7 | 0 | | 5 | 0 | 7 | 0 | 80.7 | 120.4 |
| | | 5556 | 56 | 5 | 0 | 10 | 0 | | 5 | 0 | 10 | 0 | 110.3 | 162.1 |
| | | 5557 | 56 | 8 | 0 | 9 | 0 | | 8 | 0 | 9 | 0 | 118.6 | 185.3 |
| | | 5558 | 56 | 10 | 0 | 8 | 1 | | 10 | 0 | 8 | 0 | 121.8 | 174.2 |
| | | 5559 | 56 | 7 | 0 | 8 | 0 | | 7 | 0 | 7 | 1 | 107.1 | 174.4 |
| | | 5560 | 56 | 9 | 0 | 6 | 0 | | 9 | 0 | 6 | 0 | 110.5 | 162.8 |
| | | 5562 | 56 | 8 | 0 | 4 | 0 | | 8 | 0 | 4 | 0 | 80.7 | 139.1 |
| | | 5563 | 56 | 9 | 0 | 7 | 1 | | 9 | 0 | 7 | 0 | 115.4 | 191.8 |
| 4 | f | 5564 | 56 | 2 | 0 | 3 | 0 | | 2 | 0 | 3 | 0 | 40.0 | 70.0 |
| | | 5565 | 56 | 8 | 0 | 7 | 0 | | 8 | 0 | 7 | 0 | 114.8 | 155.8 |
| | | 5566 | 56 | 10 | 2 | 7 | 1 | | 10 | 0 | 7 | 0 | 102.8 | 147.3 |
| | | 5567 | 56 | 5 | 0 | 10 | 0 | | 5 | 0 | 10 | 0 | 96.2 | 131.1 |
| | | 5568 | 56 | 2 | 0 | 2 | 0 | | 2 | 0 | 1 | 1 | 32.7 | 43.4 |
| | | 5569 | 56 | 8 | 0 | 4 | 0 | | 8 | 0 | 4 | 0 | 84.5 | 122.8 |
| | | 5590 | 56 | 6 | 0 | 11 | 0 | | 6 | 0 | 11 | 0 | 113.4 | 165.8 |
| | | 5591 | 56 | 6 | 0 | 6 | 0 | | 6 | 0 | 7 | 1 | 69.7 | 96.9 |
| | | 5592 | 56 | 2 | 0 | 13 | 0 | | 2 | 0 | 12 | 1 | 108.7 | 158.6 |
| | | 5593 | 56 | 6 | 0 | 6 | 0 | | 6 | 0 | 7 | 1 | 111.9 | 161 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix R: Individual Reproductive Parameters – Reproductive Group Female Rats

| Group Sex | Animal Number | Implant Sites | Corpora Left | Corpora Right |
|---|---|---|---|---|
| 1f | 5494 | 16 | 6 | 11 |
| | 5495 | 16 | 9 | 9 |
| | 5496 | 18 | 12 | 13 |
| | 5497 | 19 | 14 | 17 |
| | 5498 | 17 | 6 | 11 |
| | 5499 | 16 | 19 | 4 |
| | 5500 | 16 | 9 | 13 |
| | 5502 | 17 | 14 | 18 |
| | 5503 | 16 | 13 | 15 |
| | Mean | 16.8 | 11.3 | 12.3 |
| | S.D. | 1.1 | 4.2 | 4.3 |
| | N | 9 | 9 | 9 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix R: Individual Reproductive Parameters – Reproductive Group Female Rats

| Group Sex | Animal Number | Implant Sites | Corpora Left | Corpora Right |
|---|---|---|---|---|
| 2f | 5504 | 16 | 10 | 16 |
| | 5524 | 15 | 8 | 9 |
| | 5525 | 17 | 14 | 13 |
| | 5526 | 13 | 7 | 13 |
| | 5527 | 19 | 8 | 12 |
| | 5528 | 17 | 12 | 18 |
| | 5529 | 15 | 10 | 8 |
| | 5531 | 16 | 10 | 6 |
| | 5532 | 20 | 9 | 16 |
| | Mean | 16.4 | 9.8 | 12.3 |
| | S.D. | 2.1 | 2.2 | 4.0 |
| | N | 9 | 9 | 9 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix R: Individual Reproductive Parameters – Reproductive Group Female Rats

| Group Sex | Animal Number | Implant Sites | Corpora Left | Corpora Right |
|---|---|---|---|---|
| 3f | 5554 | 17 | 8 | 10 |
| | 5555 | 14 | 10 | 12 |
| | 5556 | 17 | 9 | 12 |
| | 5557 | 18 | 12 | 16 |
| | 5558 | 19 | 10 | 11 |
| | 5559 | 17 | 7 | 16 |
| | 5560 | 16 | 9 | 8 |
| | 5562 | 14 | 4 | 13 |
| | 5563 | 18 | 9 | 15 |
| | Mean | 16.7 | 8.7 | 12.6 |
| | S.D. | 1.7 | 2.2 | 2.7 |
| | N | 9 | 9 | 9 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# Appendix R: Individual Reproductive Parameters – Reproductive Group Female Rats

| Group Sex | Animal Number | Implant Sites | Corpora Left | Corpora Right |
|---|---|---|---|---|
| 4f | 5584 | 10 | 9 | 15 |
| | 5585 | 16 | 7 | 16 |
| | 5586 | 20 | 17 | 13 |
| | 5587 | 17 | 9 | 9 |
| | 5588 | 11 | 12 | 12 |
| | 5589 | 14 | 10 | 17 |
| | 5590 | 17 | 8 | 9 |
| | 5591 | 15 | 8 | 8 |
| | 5592 | 16 | 8 | 4 |
| | 5593 | 17 | 12 | 8 |
| | Mean | 15.3 | 10.0 | 11.1 |
| | S.D. | 3.0 | 3.0 | 4.2 |
| | N | 10 | 10 | 10 |

Group 1 - 0mg/kg  Group 2 - 50mg/kg  Group 3 - 250mg/kg  Group 4 - 500mg/kg

# APPENDIX S

## DOW CORNING CORPORATION
## HEALTH & ENVIRONMENTAL SCIENCES

## CONTRIBUTING SCIENTIST REPORT

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| | |
|---|---|
| **Report Title:** | Statistical Analysis for the Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test for Dimethylsilanediol (DMSD), ZMAT 4065555, in Sprague-Dawley Rats via Oral Gavage |
| **HES Study Number:** | 10872-102 |
| **Test Article:** | Dimethylsilanediol (DMSD) |
| **Contributing Scientist:** | Cynthia Van Landingham |
| **Sponsor:** | Silicones Environmental, Health and Safety Council<br>2325 Dulles Corner Blvd., Suite 500<br>Herndon, VA 20171 |
| **HES Group Manager:** | Paul A. Jean, Ph.D.<br>Team Leader, Toxicology<br>Health and Environmental Sciences |
| **Testing Facility:** | Dow Corning Corporation<br>Health and Environmental Sciences<br>2200 West Salzburg Road<br>Auburn, Michigan 48611 |
| **Analysis Start Date:** | 9/30/2008 |
| **Analysis End Date:** | 6/29/2009 |

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## APPROVAL SIGNATURES

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## OBJECTIVE

The objective of this contributing scientist report is to provide statistical analysis of the following study data: body weight and change in body weight (all study groups), food consumption (all study groups), all reproductive group female parameters, clinical signs (toxicology female and male groups), functional observation battery (toxicology female and male groups), motor activity (toxicology female and male groups), and histopathological findings (toxicology female and male groups).

## EXPERIMENTAL

Groups of 10 rats per sex per dose (toxicology male and female groups) were orally administered 0, 50, 250, or 500 mg/kg/day of dimethylsilanediol in corn oil by gavage for four weeks. An additional 10 females/dosage level were used to assess reproductive effects of the test article and these animals were administerd the treatments through post-partum day 3 (reproductive female group). One animal, female #5504 (orginally in the toxicology female group, 50 mg/kg/day), was removed from the toxicology group and used to replace a reproductive group female during the first week of the study since female #5530 was euthanized on study day 3. Therefore, in the data analysis that follows, N=9 for the 50 mg/kg/day toxicology group females. In the reproductive female groups, one animal each in the following dose groups; 0, 50 and 250 mg/kg/day (#5501, #5533 and #5561, respectively) had positive evidence of copulation and were found to be non-pregnant. In the data analysis that follows, N=9 for the reproductive groups in the post-partum phase of the study.

## DATA ANALYSIS

All data analysis was carried out using SAS version 9.1.3 [1]. Statistically significant probabilities were reported for p-values of $< 0.05$, $<0.02$, and $< 0.01$.

Body weight, changes in body weight, and food consumption data were analyzed using a one-way Analysis of Variance (ANOVA) [2] if the data satisfied the requirements of normality of the residuals and homogeneity of variance as determined using the Shapiro-Wilk [3] test for normality and Levene's test [4] for homogeneity of variance. If the data did not satisfy the parametric requirements, a Kruskal-Wallis test [5, 6] was used. If the ANOVA or Kruskal-Wallis test was significant, pair-wise comparisons of the exposed groups to control were made using the Dunnett's Test [7, 8] or a Wilcoxon test, respectively.

For variables with multiple measurements across time (motor activity, body weight and food consumption), a repeated measurements ANOVA was performed to determine if a significant time by treatment group interaction exists. Repeated measurements ANOVAs were done using the time (baseline and post-treatment), interval, sex and treatment to look for interactions between the treatment, the time and sex to determine if analysis could be done with the sexes combined. See flow chart on the analysis of motor activity.

# APPENDIX S

Reproductive Parameters with the exception of litter size and % post implantation loss were analyzed using an ANCOVA (Analysis of Covariance) with litter size as the covariate. Litter size and % post implantation loss were analyzed using an ANOVA.

Measured continuous Functional Observational Battery (FOB) data were analyzed using a combination of ANCOVA with baseline evaluations used as the covariate and repeated measures ANOVA. See flow chart on the analysis of continuous FOB data.

Categorical Functional Observational Battery (FOB) data were analyzed using the Jonckheere-Terpstra test [9]. This test is used to detect a shift in the categorical observations.

Microscopic findings were analyzed using a Cochran-Armitage trend test [10] to indicate an increasing incidence trend regardless of grade with Fisher's Exact tests [11-13] used to indicate increased incidence (non-grade specific) over the control. In addition, for those microscopic findings with one or more incidences in the control group, the graded animals only were compared using a Kruskal-Wallis test [5,6] to determine if there was an increase in severity grade between the control group and the treated groups. Pair wise comparisons of the graded only animals were done using a Wilcoxon test if the overall Kruskal-Wallis test was significant.

The Clinical Signs data were analyzed using Mixed Modeling repeated measures. Mixed models represent the fixed effect of treatments and the random effect of variability from animal to animal and observation to observation (within animal). Mixed models are generalizations of standard linear models (e.g., analysis of variance) and the SAS procedure PROC MIXED can be used in instances where every animal was not examined at every time point without loss of observations as would occur when using PROC GLM to do a repeated measurement ANOVA. The repeated measures aspect of the analysis recognizes that the variability in the responses is the result of animal-to-animal variability and of variability among the individual observations within each animal over the course of the study. Using the SAS procedure PROC MIXED, the model was defined as

Response = treatmentgrp,

where, treatmentgrp indicates the class variable associated with each treatment level, with animal within treatment group as the "subject" (where the "subject" is the unit for which there are repeated observations), and the response was a binomial variable indicating that the animal had or did not have a specific abnormal response at each time point for which examination data was available. Such a mixed model represents the mean responses as a function of the treatment group with variation (standard errors) that account for animal-to-animal and within-animal variability. As in an analysis of variance, the treatment groups were examined to determine if there was an overall "treatment effect" and, if there was, then pair-wise comparisons of the individual exposed groups to the control group were completed.

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## DEVIATIONS

There were no deviations in the statistical methods used, for the summitted data, from the approved study protocol.

## RESULTS AND DISCUSSION/CONCLUSIONS

Body Weights

Body weight analysis was done on all three groups: reproductive females group (Table 1), toxicity females (Table 2) and toxicity males (Table 3). ANOVA was used for the analysis of body weight data for all days except gestation day 20 in the reproductive females and days 29 and 30 in the toxicity males which was analyzed using a Kruskal-Wallis test due to non-normality. There were no significant differences across treatment groups in the mean body weights on any day on which they were measured. The repeated measures over time analysis for the reproductive females excluded day 22 because only one animal in the 250 mg/kg/day group and one animal in the 500 mg/kg/day group were weighed. This analysis did not show a significant interaction between treatment and time for the reproductive group ($p=0.0746$) nor was there a significant interaction between treatment and time in the repeated measures analysis of body weights of the the toxicity females ($p=0.0948$) or the toxicity males ($p=0.3093$)

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**Table 1**
**Reproductive Females**
**Body Weight (g)**

| Time | | Control (0 mg/kg/day) | 50 mg/kg/day | 250 mg/kg/day | 500 mg/kg/day |
|---|---|---|---|---|---|
| Day 1 | Mean | 210.3 | 211.7 | 216.2 | 210.4 |
| | Std | 7.5 | 11.9 | 12.1 | 11.0 |
| | N | 10 | 10 | 10 | 10 |
| Day 8 | Mean | 232.8 | 228.2 | 236.5 | 231.5 |
| | Std | 9.6 | 13.4 | 14.1 | 16.4 |
| | N | 10 | 10 | 10 | 10 |
| Day 15 | Mean | 251.8 | 244.2 | 255.1 | 244.9 |
| | Std | 9.7 | 21.0 | 14.1 | 20.7 |
| | N | 10 | 10 | 10 | 10 |
| Day 22 | Mean | | | 274.9 | 230.6 |
| | Std | | | | |
| | N | | | 1 | 1 |
| Gestation Day 0 | Mean | 259.0 | 253.2 | 261.4 | 255.2 |
| | Std | 14.4 | 16.8 | 12.9 | 21.6 |
| | N | 10 | 10 | 10 | 10 |
| Gestation Day 7 | Mean | 292.7 | 281.1 | 289.4 | 286.4 |
| | Std | 11.9 | 19.0 | 19.5 | 18.7 |
| | N | 10 | 10 | 10 | 10 |
| Gestation Day 14 | Mean | 331.8 | 320.8 | 328.6 | 317.9 |
| | Std | 18.9 | 25.6 | 27.9 | 24.0 |
| | N | 10 | 10 | 10 | 10 |
| Gestation Day 20 | Mean | 416.6 | 405.3 | 408.8 | 396.8 |
| | Std | 43.2 | 44.8 | 56.7 | 38.3 |
| | N | 10 | 10 | 10 | 10 |
| Post-Partum Day 0 | Mean | 322.9 | 314.9 | 317.1 | 299.3 |
| | Std | 16.7 | 21.6 | 22.8 | 21.1 |
| | N | 10 | 10 | 10 | 10 |
| Terminal Sacrifice | Mean | 340.1 | 330.3 | 332.5 | 324.3 |
| | Std | 13.1 | 27.1 | 24.6 | 25.0 |
| | N | 9 | 9 | 9 | 10 |

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**Table 2**
**Toxicity Females**
**Body Weight (g)**

| Time | | Control (0 mg/kg/day) | 50 mg/kg/day | 250 mg/kg/day | 500 mg/kg/day |
|---|---|---|---|---|---|
| Day 1 | Mean | 211.4 | 210.7 | 211.7 | 209.0 |
| | Std | 12.5 | 10.2 | 14.4 | 14.0 |
| | N | 10 | 9 | 10 | 10 |
| Day 8 | Mean | 231.3 | 226.8 | 231.2 | 232.3 |
| | Std | 17.8 | 16.3 | 13.6 | 22.6 |
| | N | 10 | 9 | 10 | 10 |
| Day 15 | Mean | 248.5 | 242.8 | 249.8 | 249.2 |
| | Std | 23.6 | 18.7 | 17.4 | 20.4 |
| | N | 10 | 9 | 10 | 10 |
| Day 22 | Mean | 267.9 | 262.7 | 265.0 | 259.2 |
| | Std | 24.7 | 23.9 | 19.6 | 23.9 |
| | N | 10 | 9 | 10 | 10 |
| Day 28 | Mean | 274.7 | 271.6 | 270.5 | 268.8 |
| | Std | 24.6 | 22.6 | 15.6 | 22.2 |
| | N | 10 | 9 | 10 | 10 |
| Day 29 | Mean | 259.6 | 256.3 | 258.0 | 254.5 |
| | Std | 24.1 | 21.7 | 16.6 | 21.5 |
| | N | 10 | 9 | 10 | 10 |

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| Table 3<br>Toxicity Males<br>Body Weight (g) | | | | | |
|---|---|---|---|---|---|
| Time | | Control (0 mg/kg/day) | 50 mg/kg/day | 250 mg/kg/day | 500 mg/kg/day |
| Day 1 | Mean | 310.2 | 310.5 | 303.3 | 310.2 |
| | Std | 9.4 | 9.7 | 8.7 | 14.3 |
| | N | 10 | 10 | 10 | 10 |
| Day 8 | Mean | 352.4 | 352.1 | 345.4 | 350.9 |
| | Std | 9.9 | 13.7 | 17.6 | 18.0 |
| | N | 10 | 10 | 10 | 10 |
| Day 15 | Mean | 391.0 | 388.8 | 382.9 | 382.0 |
| | Std | 14.7 | 20.0 | 21.2 | 22.7 |
| | N | 10 | 10 | 10 | 10 |
| Day 22 | Mean | 425.1 | 421.1 | 413.8 | 404.9 |
| | Std | 19.5 | 31.0 | 25.3 | 25.5 |
| | N | 10 | 10 | 10 | 10 |
| Day 29 | Mean | 452.8 | 444.2 | 441.8 | 420.1 |
| | Std | 26.6 | 32.5 | 27.3 | 30.7 |
| | N | 10 | 10 | 10 | 10 |
| Day 30 | Mean | 430.8 | 421.5 | 420.2 | 401.2 |
| | Std | 24.5 | 32.0 | 25.1 | 26.6 |
| | N | 10 | 10 | 10 | 10 |

Change in Body Weights

As with the body weights, change in body weight analysis was done for all three groups: the reproductive females (Table 4), the toxicity females (Table 5) and the toxicity males (Table 6). ANOVA was used for the change in body weight analysis for each time period except for the gestation weeks 2 and 3 in the reproductive females and week 4 for the toxicity males. These time periods were analyzed with a Kruskal-Wallis test due to non-normality.

There were no statistically significant differences between the treated and control groups in change in body weight for any time period analyzed for the reproductive females. For the toxicity females, the increase in body weight in week 3 was significantly larger in the control group than in the 500 mg/kg/day group. For the toxicity males, there were differences seen in week 4 with the control group gaining significantly more weight than the 500 mg/kg/day group and the overall weight change from day 1 to day 29 was also significantly different across the dose groups. For the total weight change from day 1 to day 29 in the males, the control group gained significantly more weight than the 500 mg/kg/day group.

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**Table 4**
**Reproductive Females**
**Change in Body Weight (g)**

| Time | | Control (0 mg/kg/day) | 50 mg/kg/day | 250 mg/kg/day | 500 mg/kg/day |
|---|---|---|---|---|---|
| Week 1 | Mean | 22.5 | 16.6 | 20.3 | 21.0 |
| | Std | 5.4 | 4.0 | 8.1 | 7.8 |
| | N | 10 | 10 | 10 | 10 |
| Week 2 | Mean | 19.0 | 15.9 | 18.7 | 13.4 |
| | Std | 4.6 | 8.5 | 7.4 | 6.0 |
| | N | 10 | 10 | 10 | 10 |
| Total by Day 29 | Mean | 48.7 | 41.5 | 45.2 | 44.8 |
| | Std | 9.7 | 7.8 | 7.3 | 13.3 |
| | N | 10 | 10 | 10 | 10 |
| Gestation Week 1 | Mean | 33.7 | 27.9 | 28.0 | 31.2 |
| | Std | 5.3 | 8.0 | 9.9 | 5.4 |
| | N | 10 | 10 | 10 | 10 |
| Gestation Week 2 | Mean | 39.1 | 39.8 | 39.2 | 31.4 |
| | Std | 11.1 | 9.9 | 11.1 | 7.5 |
| | N | 10 | 10 | 10 | 10 |
| Gestation Week 3 | Mean | 84.8 | 84.4 | 80.2 | 78.9 |
| | Std | 27.7 | 26.4 | 31.0 | 23.4 |
| | N | 10 | 10 | 10 | 10 |
| Post-Partum | Mean | 15.0 | 15.6 | 11.8 | 25.0 |
| | Std | 7.8 | 14.6 | 7.8 | 10.6 |
| | N | 9 | 9 | 9 | 10 |
| Total by Post-Partum Day 4 | Mean | 129.3 | 118.8 | 115.7 | 113.9 |
| | Std | 11.1 | 21.1 | 16.9 | 16.6 |
| | N | 9 | 9 | 9 | 10 |

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**Table 5**
**Toxicity Females**
**Change in Body Weight (g)**

| Time | | Control (0 mg/kg/day) | | 50 mg/kg/day | | 250 mg/kg/day | | 500 mg/kg/day | |
|---|---|---|---|---|---|---|---|---|---|
| Week 1 | Mean | 19.9 | | 16.1 | | 19.5 | | 23.3 | |
| | Std | 7.0 | | 7.2 | | 4.0 | | 10.4 | |
| | N | 10 | | 9 | | 10 | | 10 | |
| Week 2 | Mean | 17.2 | | 16.0 | | 18.6 | | 16.9 | |
| | Std | 7.3 | | 4.6 | | 6.6 | | 4.6 | |
| | N | 10 | | 9 | | 10 | | 10 | |
| Week 3 | Mean | 19.4 | ** | 19.8 | | 15.1 | | 10.0 | ** |
| | Std | 7.6 | | 7.3 | | 7.2 | | 5.7 | |
| | N | 10 | | 9 | | 10 | | 10 | |
| Week 4 | Mean | 6.8 | | 9.0 | | 5.5 | | 9.7 | |
| | Std | 4.6 | | 3.6 | | 5.7 | | 5.6 | |
| | N | 10 | | 9 | | 10 | | 10 | |
| Total by Day 28 | Mean | 63.3 | | 60.9 | | 58.7 | | 59.8 | |
| | Std | 15.3 | | 15.0 | | 9.2 | | 9.9 | |
| | N | 10 | | 9 | | 10 | | 10 | |

Asterisks indicate a significant difference across treatment groups (in the control column) or between control and a treatment group with p-values of * < 0.05, ** < 0.02 or *** < 0.01.

**Table 6**
**Toxicity Males**
**Change in Body Weight (g)**

| Time | | Control (0 mg/kg/day) | | 50 mg/kg/day | | 250 mg/kg/day | | 500 mg/kg/day | |
|---|---|---|---|---|---|---|---|---|---|
| Week 1 | Mean | 42.2 | | 41.6 | | 42.0 | | 40.7 | |
| | Std | 6.1 | | 8.5 | | 13.6 | | 8.4 | |
| | N | 10 | | 10 | | 10 | | 10 | |
| Week 2 | Mean | 38.6 | | 36.8 | | 37.5 | | 31.1 | |
| | Std | 8.1 | | 9.6 | | 8.9 | | 7.5 | |
| | N | 10 | | 10 | | 10 | | 10 | |
| Week 3 | Mean | 34.2 | | 32.3 | | 31.0 | | 22.9 | |
| | Std | 7.7 | | 13.3 | | 10.2 | | 7.5 | |
| | N | 10 | | 10 | | 10 | | 10 | |
| Week 4 | Mean | 27.6 | * | 23.1 | | 28.0 | | 15.2 | * |
| | Std | 9.4 | | 4.1 | | 6.9 | | 19.3 | |
| | N | 10 | | 10 | | 10 | | 10 | |
| Total by Day 29 | Mean | 142.6 | * | 133.7 | | 138.5 | | 109.9 | ** |
| | Std | 25.0 | | 28.4 | | 23.0 | | 24.5 | |
| | N | 10 | | 10 | | 10 | | 10 | |

Asterisks indicate a significant difference across treatment groups (in the control column) or between control and a treatment group with p-values of * < 0.05, ** < 0.02 or *** < 0.01.

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Food Consumption

Analysis of food consumption data were done for all three groups, the reproductive females, the toxicology females, and the toxicology males. For the total grams of food, the first week was estimated for animals in the toxicology female control and male control that had their daily values calculated from only 3 days (day 5 to day 8). This estimation was done by adding in 4 times the average daily value to the difference between days 5 and 8.

ANOVAs were used to analyze the data for all three groups except for gestation week 3 in the female reproductive group and the week 4 for the toxicology females which were analyzed using a Kruskal-Wallis test due to non-normality. There were no differences seen in the average daily food consumption across treatment groups for the female reproductive group (Table 7) or the female toxicology group (Table 8). There were significant differences in food consumption among the male toxicology group during week 2 (Table 9), however, pair wise comparisons between the treatment groups and control did not show any statistically significant differences. The repeated measures analysis showed no significant time by treatment interactions for the reproductive group females (p=0.1662) or for the female toxicology group (p=0.0759). No repeated measures analysis was conducted on the male toxicology food consumption data since there were only two time points.

**Table 7**
**Reproductive Females**
**Average Daily Food Consumption (g/day)**

| Time | | Control (0 mg/kg/day) | 50 mg/kg/day | 250 mg/kg/day | 500 mg/kg/day |
|---|---|---|---|---|---|
| Pre-Mating Week 1 | Mean | 18.2 | 18.6 | 19.4 | 17.6 |
| | Std | 1.4 | 2.0 | 1.5 | 2.7 |
| | N | 10 | 10 | 10 | 10 |
| Pre-Mating Week 2 | Mean | 18.6 | 18.7 | 19.9 | 17.4 |
| | Std | 1.0 | 2.5 | 1.8 | 2.1 |
| | N | 10 | 10 | 10 | 10 |
| Gestational Week 1 | Mean | 19.3 | 18.7 | 18.1 | 18.0 |
| | Std | 1.4 | 2.4 | 2.3 | 2.1 |
| | N | 10 | 10 | 10 | 10 |
| Gestational Week 2 | Mean | 20.6 | 20.7 | 19.6 | 18.8 |
| | Std | 1.5 | 2.1 | 3.2 | 1.9 |
| | N | 10 | 10 | 10 | 10 |
| Gestational Week 3 | Mean | 22.7 | 23.1 | 22.5 | 22.2 |
| | Std | 2.2 | 3.0 | 4.1 | 2.9 |
| | N | 10 | 10 | 10 | 10 |
| Post-Partum Days 0-4 | Mean | 35.0 | 34.9 | 32.2 | 32.5 |
| | Std | 3.3 | 5.5 | 5.5 | 7.3 |
| | N | 9 | 9 | 9 | 10 |

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**Table 8**
**Toxicology Females**
**Average Daily Food Consumption (g/day)**

| Time | | Control (0 mg/kg/day) | 50 mg/kg/day | 250 mg/kg/day | 500 mg/kg/day |
|---|---|---|---|---|---|
| Week 1 | Mean | 18.8 | 17.1 | 17.7 | 17.3 |
| | Std | 3.2 | 2.4 | 1.5 | 2.2 |
| | N | 10 | 9 | 10 | 10 |
| Week 2 | Mean | 19.2 | 17.5 | 18.6 | 18.5 |
| | Std | 2.6 | 1.6 | 2.0 | 1.9 |
| | N | 10 | 9 | 10 | 10 |
| Week 3 | Mean | 19.6 | 18.0 | 17.8 | 17.9 |
| | Std | 2.6 | 2.0 | 1.9 | 1.5 |
| | N | 10 | 9 | 10 | 10 |
| Week 4 | Mean | 17.5 | 17.0 | 16.6 | 16.4 |
| | Std | 3.1 | 1.7 | 1.7 | 1.9 |
| | N | 10 | 9 | 10 | 10 |
| Total (g) | Mean | 507.6 | 470.6 | 478.3 | 474.2 |
| | Std | 72.9 | 48.7 | 45.0 | 43.6 |
| | N | 10 | 9 | 10 | 10 |

**Table 9**
**Toxicology Males**
**Average Daily Food Consumption (g/day)**

| Time | | Control (0 mg/kg/day) | 50 mg/kg/day | 250 mg/kg/day | 500 mg/kg/day |
|---|---|---|---|---|---|
| Week 1 | Mean | 25.9 | 26.0 | 25.3 | 23.7 |
| | Std | 1.9 | 2.1 | 2.6 | 2.2 |
| | N | 10 | 10 | 10 | 10 |
| Week 2 | Mean | 24.7 * | 25.4 | 24.9 | 22.6 |
| | Std | 2.1 | 2.5 | 2.2 | 2.1 |
| | N | 10 | 10 | 10 | 10 |
| Total (g) | Mean | 353.6 | 359.1 | 351.7 | 324.5 |
| | Std | 27.4 | 31.2 | 31.0 | 29.5 |
| | N | 10 | 10 | 10 | 10 |

Asterisks indicate a significant difference across treatment groups (in the control column) or between control and a treatment group with p-values of * < 0.05, ** < 0.02 or *** < 0.01.

Reproductive Values

Reproductive values (Table 10) from the female reproductive groups were analyzed using an ANOVA for the litter size and % post implantation loss and ANCOVA for all other endpoints using litter size as a covariate. There were no significant differences across treatments. The litter size was a significant variable for several of the reproductive

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parameters, and the treatment was a significant variable for the day 4 viable pups, the viable/total and the total implants and the male/female ratio and the interaction between the treatment and litter size was also significant for day 4 viable pups (p=0.0063), the viable/total (p=0.0125) and the total implants (p=0.0222) but was not significant for any other endpoint. Pair wise comparisons which adjust for the litter size and compare treated versus control did not find any statistically significant differences.

**Table 10**
**Reproductive Females**
**Reproductive Measurements**

| | | Control (0 mg/kg/day) | | 50 mg/kg/day | | 250 mg/kg/day | | 500 mg/kg/day | | Litter Size Significance |
|---|---|---|---|---|---|---|---|---|---|---|
| Average Litter Size | Mean | 16 | | 15 | | 15 | | 13 | | |
| | Std | 2 | | 2 | | 2 | | 5 | | |
| | N | 9 | | 9 | | 9 | | 10 | | |
| %Post Implantation Loss | Mean | 9.4 | | 7.5 | | 10.3 | | 19.2 | | |
| | Std | 14.0 | | 6.0 | | 3.6 | | 20.8 | | |
| | N | 9 | | 9 | | 9 | | 10 | | |
| Days Gestation | Mean | 22 | | 22 | | 22 | | 23 | | |
| | Std | 0.6 | | 0.3 | | 0.5 | | 0.0 | | |
| | N | 9 | | 9 | | 9 | | 10 | | |
| Male Pups | Mean | 9 | | 8 | | 8 | | 6 | | *** |
| | Std | 2 | | 2 | | 2 | | 3 | | |
| | N | 9 | | 9 | | 9 | | 10 | | |
| Female Pups | Mean | 7 | | 7 | | 7 | | 7 | | *** |
| | Std | 1 | | 2 | | 2 | | 4 | | |
| | N | 9 | | 9 | | 9 | | 10 | | |
| Males/Females | Mean | 1.2 | | 1.2 | | 1.4 | | 0.9 | | |
| | Std | 0.3 | | 0.5 | | 1.1 | | 0.5 | | |
| | N | 9 | | 9 | | 9 | | 10 | | |
| Day 4 Viable Pups | Mean | 15 | *** | 15 | | 15 | | 12 | | *** |
| | Std | 3 | | 2 | | 2 | | 5 | | |
| | N | 9 | | 9 | | 9 | | 10 | | |
| Viable/Total | Mean | 0.95 | ** | 0.98 | | 0.98 | | 0.94 | | * |
| | Std | 0.11 | | 0.03 | | 0.03 | | 0.08 | | |
| | N | 9 | | 9 | | 9 | | 10 | | |
| Initial Litter Weight (g) | Mean | 101.6 | | 102.5 | | 104.8 | | 89.5 | | *** |
| | Std | 17.0 | | 12.6 | | 15.3 | | 29.8 | | |
| | N | 9 | | 9 | | 9 | | 10 | | |
| Initial Average Pup Weight (g) | Mean | 6.7 | | 6.8 | | 7.0 | | 7.2 | | * |
| | Std | 0.4 | | 0.2 | | 0.3 | | 0.8 | | |
| | N | 9 | | 9 | | 9 | | 10 | | |
| Final Litter Weight (g) | Mean | 168.5 | | 163.1 | | 163.3 | | 125.3 | | *** |
| | Std | 25.8 | | 17.9 | | 22.3 | | 42.3 | | |
| | N | 9 | | 9 | | 9 | | 10 | | |

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| Table 10 (continued) Reproductive Females Reproductive Measurements | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Control (0 mg/kg/day) | | 50 mg/kg/day | | 250 mg/kg/day | | 500 mg/kg/day | | Litter Size Significance |
| Final Average Pup Weight (g) | Mean | 11.4 | | 10.9 | | 11.0 | | 10.7 | | *** |
| | Std | 1.6 | | 0.8 | | 0.9 | | 2.3 | | |
| | N | 9 | | 9 | | 9 | | 10 | | |
| Total Implants | Mean | 17 | * | 16 | | 17 | | 15 | | *** |
| | Std | 1 | | 2 | | 2 | | 3 | | |
| | N | 9 | | 9 | | 9 | | 10 | | |
| Corpora Lutea Counts | Mean | 24 | | 22 | | 21 | | 21 | | |
| | Std | 6 | | 5 | | 4 | | 5 | | |
| | N | 9 | | 9 | | 9 | | 10 | | |
| %Post Natal Loss | Mean | 1.2 | | 1.4 | | 0.7 | | 4.6 | | |
| | Std | 3.7 | | 2.7 | | 2.2 | | 7.9 | | |
| | N | 9 | | 9 | | 9 | | 10 | | |

Note: Asterisks next to the control indicate a significant treatment effect in the ANCOVA, asterisks in the litter column indicate a significant litter effect in the ANCOVA with p-values of * < 0.05, ** < 0.02 or *** <0.01. There are no significant differences between the control and the treated group by Dunnett's test after adjusting for litter size.

Functional Observational Battery (FOB) Continuous Values

Collected baseline data for animal #5504, originally in the female toxicology group (50 mg/kg/day), was not used in the statistical analysis since there was not a treated FOB continous counterpart. The FOB continuous data for toxicology group females (Table 11) and males (Table 12) were homogeneous and normally distributed with the sexes combined at the alpha = 0.01 level. The ANCOVA with treatment by sex and treatment by covariate (baseline measurement) showed a significant treatment by sex interaction for the hindlimb grip strength (p=0.0058), the rectal temperature (p=0.0001) and the landing foot splay (p=0.0396) but not for the forelimb grip strength (p=0.4521). The baseline by treatment interaction in the ANCOVA was not significant for the forelimb grip strength (p=0.7065). When the sexes were separated for the hindlimb grip, rectal temperature and landing foot splay, the data was homogeneous and normally distributed. The ANCOVAs on the sex separated data showed no significant treatment by baseline interaction for hindlimb grip (females p=0.2494, males p=0.8959), the rectal temperature (females p=0.0905, males p=0.4346), or the landing foot splay (females p=0.8116, males p=0.4680). Therefore, the ANCOVA was used for the analyses.

The sex combined ANCOVA for the forelimb grip strength showed no treatment effect (p=0.6842) nor did sexes separated ANCOVAs for the hindlimb grip (females p=0.2861, males p=0.8178), the rectal temperature (females p=0.091, males p=0.4272) or the landing foot splay (females p=0.6351, males p=0.4197).

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**Table 11**
**Females**
**FOB Continuous**

| Endpoint | Time | | Control (0 mg/kg/day) | 50 mg/kg/day | 250 mg/kg/day | 500 mg/kg/day |
|---|---|---|---|---|---|---|
| Forelimb Grip Strength (g) | Baseline | Mean | 721.8 | 737.2 | 721.3 | 743.7 |
| | | Std | 69.6 | 91.7 | 86.4 | 81.0 |
| | | N | 10 | 9 | 10 | 10 |
| | Treated | Mean | 866.0 | 975.9 | 992.5 | 990.2 |
| | | Std | 170.6 | 145.6 | 237.3 | 178.3 |
| | | N | 10 | 9 | 10 | 10 |
| Hindlimb Grip Strength (g) | Baseline | Mean | 693.2 | 649.4 | 681.5 | 719.0 |
| | | Std | 119.1 | 101.6 | 107.7 | 163.2 |
| | | N | 10 | 9 | 10 | 10 |
| | Treated | Mean | 1005.5 | 1019.3 | 1108.3 | 985.7 |
| | | Std | 138.2 | 105.7 | 193.1 | 225.6 |
| | | N | 10 | 9 | 10 | 10 |
| Landing Foot Splay (cm) | Baseline | Mean | 10.8 | 10.6 | 10.9 | 10.9 |
| | | Std | 1.0 | 2.2 | 1.8 | 1.9 |
| | | N | 10 | 9 | 10 | 10 |
| | Treated | Mean | 9.8 | 11.4 | 10.1 | 10.5 |
| | | Std | 1.5 | 2.0 | 1.3 | 1.9 |
| | | N | 10 | 9 | 10 | 10 |
| Rectal Temperature (°Celsius) | Baseline | Mean | 38.1 | 38.0 | 37.9 | 38.0 |
| | | Std | 0.6 | 0.3 | 0.4 | 0.4 |
| | | N | 10 | 9 | 10 | 10 |
| | Treated | Mean | 38.2 | 38.4 | 38.4 | 38.5 |
| | | Std | 0.4 | 0.3 | 0.3 | 0.3 |
| | | N | 10 | 9 | 10 | 10 |

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| Table 12<br>Males<br>FOB Continuous | | | | | | |
|---|---|---|---|---|---|---|
| **Endpoint** | **Time** | | **Control (0 mg/kg/day)** | **50 mg/kg/day** | **250 mg/kg/day** | **500 mg/kg/day** |
| Forelimb Grip Strength (g) | Baseline | Mean | 818.5 | 809.3 | 745.2 | 813.5 |
| | | Std | 143.0 | 141.6 | 90.2 | 166.4 |
| | | N | 10 | 10 | 10 | 10 |
| | Treated | Mean | 1077.0 | 1111.7 | 1022.2 | 992.5 |
| | | Std | 258.8 | 188.8 | 268.9 | 163.4 |
| | | N | 10 | 10 | 10 | 10 |
| Hindlimb Grip Strength (g) | Baseline | Mean | 814.5 | 750.9 | 704.8 | 716.4 |
| | | Std | 145.8 | 114.9 | 130.2 | 111.5 |
| | | N | 10 | 10 | 10 | 10 |
| | Treated | Mean | 1249.5 | 1222.0 | 1235.5 | 1065.2 |
| | | Std | 126.7 | 150.8 | 165.5 | 180.2 |
| | | N | 10 | 10 | 10 | 10 |
| Landing Foot Splay (cm) | Baseline | Mean | 13.4 | 13.2 | 13.4 | 12.0 |
| | | Std | 1.4 | 1.3 | 1.7 | 2.0 |
| | | N | 10 | 10 | 10 | 10 |
| | Treated | Mean | 13.2 | 11.9 | 11.8 | 12.0 |
| | | Std | 2.2 | 1.5 | 1.5 | 1.5 |
| | | N | 10 | 10 | 10 | 10 |
| Rectal Temperature (°Celsius) | Baseline | Mean | 37.5 | 37.6 | 37.7 | 37.7 |
| | | Std | 0.5 | 0.5 | 0.3 | 0.4 |
| | | N | 10 | 10 | 10 | 10 |
| | Treated | Mean | 38.0 | 38.0 | 37.9 | 37.8 |
| | | Std | 0.5 | 0.4 | 0.2 | 0.4 |
| | | N | 10 | 10 | 10 | 10 |

Functional Observational Battery (FOB) Categorical Data

Collected baseline data for animal #5504, originally in the female toxicology group (50 mg/kg/day), was not used in the statistical analysis since there was not a treated FOB categorical counterpart. There were no statistically significant differences across dose groups in either the baseline or treated FOB categorical data for the toxicology group females (Table 13). For the males, there were statistically significant differences across groups for the baseline response to sharp noise and treated defecation. There were no pair wise differences between the control and any treated groups for the baseline response to sharp noise but the defection in the 500 mg/kg/day group after treatment was statistically significantly higher than did control group's (Table 14).

# APPENDIX S

**Table 13**
**Toxicology Females**
**FOB Ranked**

| Endpoint | Time | #Examined / Response | Control (0 mg/kg/day) | 50 mg/kg/day | 250 mg/kg/day | 500 mg/kg/day |
|---|---|---|---|---|---|---|
| Resistance to Removal | Baseline | # Examined | 10 | 9 | 10 | 10 |
| | | Moderate; actively avoids capture but is not aggressive | 10 | 7 | 10 | 10 |
| | | Pronounced; actively avoids capture and/or is mildly aggressive | 0 | 2 | 0 | 0 |
| | Treated | # Examined | 10 | 9 | 10 | 10 |
| | | Minimally avoids capture but is not aggressive | 1 | 0 | 0 | 0 |
| | | Moderate; actively avoids capture but is not aggressive | 9 | 9 | 10 | 10 |
| Palpebral Closure | Baseline | # Examined | 10 | 9 | 10 | 10 |
| | | Open | 10 | 9 | 10 | 10 |
| | Treated | # Examined | 10 | 9 | 10 | 10 |
| | | Open | 10 | 9 | 10 | 10 |
| Pupil Reactivity | Baseline | # Examined | 10 | 9 | 10 | 10 |
| | | Dilated, briskly reactive pupil | 10 | 9 | 10 | 10 |
| | Treated | # Examined | 10 | 9 | 10 | 10 |
| | | Dilated, briskly reactive pupil | 10 | 9 | 10 | 10 |
| Pupil Size | Baseline | # Examined | 10 | 9 | 10 | 10 |
| | | Normal pupil size | 10 | 9 | 10 | 10 |
| | Treated | # Examined | 10 | 9 | 10 | 10 |
| | | Normal pupil size | 10 | 9 | 10 | 10 |
| Lacrimation | Baseline | # Examined | 10 | 9 | 10 | 10 |
| | | Glistening cornea | 10 | 9 | 10 | 10 |
| | Treated | # Examined | 10 | 9 | 10 | 10 |
| | | Glistening cornea | 10 | 9 | 10 | 10 |

**Table 13 (continued)**
**Toxicology Females**
**FOB Ranked**

| Endpoint | Time | #Examined / Response | Control (0 mg/kg/day) | 50 mg/kg/day | 250 mg/kg/day | 500 mg/kg/day |
|---|---|---|---|---|---|---|
| Salivation | Baseline | # Examined | 10 | 9 | 10 | 10 |
| | | Glistening oral cavity/lips, no wetness | 10 | 9 | 10 | 10 |
| | Treated | # Examined | 10 | 9 | 10 | 10 |
| | | Glistening oral cavity/lips, no wetness | 10 | 9 | 10 | 10 |
| Muscle Tone | Baseline | # Examined | 10 | 9 | 10 | 10 |
| | | Moderate; animal is neither very relaxed nor tense | 10 | 9 | 10 | 10 |
| | Treated | # Examined | 10 | 9 | 10 | 10 |
| | | Moderate; animal is neither very relaxed nor tense | 10 | 9 | 10 | 10 |
| Extensor Thrust | Baseline | # Examined | 10 | 9 | 10 | 10 |
| | | Moderate; clearly detectable | 10 | 9 | 10 | 10 |
| | Treated | # Examined | 10 | 9 | 10 | 10 |
| | | Moderate; clearly detectable | 10 | 9 | 10 | 10 |
| Reactivity to Handling | Baseline | # Examined | 10 | 9 | 10 | 10 |
| | | Moderate struggling with little or no vocalization | 9 | 8 | 10 | 10 |
| | | Pronounced struggling, animal may vocalize | 1 | 1 | 0 | 0 |
| | Treated | # Examined | 10 | 9 | 10 | 10 |
| | | Moderate struggling with little or no vocalization | 10 | 9 | 10 | 10 |
| Level of Activity | Baseline | # Examined | 10 | 9 | 10 | 10 |
| | | Moderate; inactive less than 50% of the time | 10 | 9 | 10 | 10 |
| | Treated | # Examined | 10 | 9 | 10 | 10 |
| | | Minimal; inactive more than 50% of the time | 1 | 0 | 0 | 0 |
| | | Moderate; inactive less than 50% of the time | 9 | 8 | 10 | 10 |
| | | Pronounced; leaves circle, occasional inactivity. | 0 | 1 | 0 | 0 |

# APPENDIX S

**Table 13 (continued)**
**Toxicology Females**
**FOB Ranked**

| Endpoint | Time | #Examined / Response | Control (0 mg/kg/day) | | 50 mg/kg/day | | 250 mg/kg/day | | 500 mg/kg/day | |
|---|---|---|---|---|---|---|---|---|---|---|
| Response to Sharp Noise | Baseline | # Examined | 10 | | 9 | | 10 | | 10 | |
| | | Moderate; clear movement of the head, neck, ears and possibly shoulders/upper body | 8 | | 8 | | 9 | | 8 | |
| | | Pronounced; clear movement of head, neck and ears, plus clear movement of whole body. | 2 | | 1 | | 1 | | 2 | |
| | Treated | # Examined | 10 | | 9 | | 10 | | 10 | |
| | | Moderate; clear movement of the head, neck, ears and possibly shoulders/upper body | 6 | | 4 | | 8 | | 6 | |
| | | Pronounced; clear movement of head, neck and ears, plus clear movement of whole body. | 4 | | 5 | | 2 | | 3 | |
| | | Exaggerated; whole body response to stimulus more intense than "pronounced"; includes whole body going airborne | 0 | | 0 | | 0 | | 1 | |
| Response to Touch | Baseline | # Examined | 10 | | 9 | | 10 | | 10 | |
| | | Moderate; spontaneously lifts tail when touched | 10 | | 8 | | 9 | | 10 | |
| | | Pronounced; spontaneously lifts tail and acts startled | 0 | | 1 | | 1 | | 0 | |
| | Treated | # Examined | 10 | | 9 | | 10 | | 10 | |
| | | Moderate; spontaneously lifts tail when touched | 10 | | 9 | | 10 | | 10 | |
| Response to Tail Pinch | Baseline | # Examined | 10 | | 9 | | 10 | | 10 | |
| | | Minimal; animal flinches and may vocalize slightly | 0 | | 0 | | 1 | | 0 | |
| | | Moderate; animal flinches, moves rapidly and/or vocalizes | 10 | | 9 | | 9 | | 10 | |
| | Treated | # Examined | 10 | | 9 | | 10 | | 10 | |
| | | Moderate; animal flinches, moves rapidly and/or vocalizes | 10 | | 9 | | 10 | | 10 | |
| Gait Evaluation | Baseline | # Examined | 10 | | 9 | | 10 | | 10 | |
| | | Smooth and coordinated gait | 10 | | 9 | | 10 | | 10 | |
| | Treated | # Examined | 10 | | 9 | | 10 | | 10 | |
| | | Smooth and coordinated gait | 10 | | 9 | | 10 | | 10 | |

# APPENDIX S

**Table 13 (continued)**
**Toxicology Females**
**FOB Ranked**

| Endpoint | Time | #Examined / Response | Control (0 mg/kg/day) | | 50 mg/kg/day | | 250 mg/kg/day | | 500 mg/kg/day | |
|---|---|---|---|---|---|---|---|---|---|---|
| Urination | Baseline | # Examined | 10 | | 9 | | 10 | | 10 | |
| | | No drops of urine | 5 | | 2 | | 1 | | 2 | |
| | | Minimal; a few (1-4) small drops or a small pool (~1 cm) | 4 | | 6 | | 6 | | 6 | |
| | | Moderate; a few (1-4) small pools or a moderate pool (2-3 cm) | 0 | | 0 | | 3 | | 2 | |
| | | Exaggerated; >4 moderate pools or a single pool >5 cm | 1 | | 1 | | 0 | | 0 | |
| | Treated | # Examined | 10 | | 9 | | 10 | | 10 | |
| | | No drops of urine | 1 | | 2 | | 4 | | 1 | |
| | | Minimal; a few (1-4) small drops or a small pool (~1 cm) | 4 | | 4 | | 4 | | 7 | |
| | | Moderate; a few (1-4) small pools or a moderate pool (2-3 cm) | 4 | | 3 | | 1 | | 1 | |
| | | Pronounced; a few (1-4) moderate pools or a large pool (4-5 cm) | 1 | | 0 | | 0 | | 1 | |
| | | Exaggerated; >4 moderate pools or a single pool >5 cm | 0 | | 0 | | 1 | | 0 | |
| Defecation | Baseline | # Examined | 10 | | 9 | | 10 | | 10 | |
| | | No pellets voided | 8 | | 9 | | 9 | | 9 | |
| | | Minimal; 1 or 2 pellets voided | 2 | | 0 | | 0 | | 1 | |
| | | Exaggerated; 5 or more pellets voided | 0 | | 0 | | 1 | | 0 | |
| | Treated | # Examined | 10 | | 9 | | 10 | | 10 | |
| | | No pellets voided | 7 | | 6 | | 8 | | 6 | |
| | | Minimal; 1 or 2 pellets voided | 2 | | 0 | | 2 | | 1 | |
| | | Moderate; 3 pellets voided | 1 | | 2 | | 0 | | 1 | |
| | | Pronounced; 4 pellets voided | 0 | | 0 | | 0 | | 1 | |
| | | Exaggerated; 5 or more pellets voided | 0 | | 1 | | 0 | | 1 | |

**Table 14**
**Males**
**FOB Ranked**

| Endpoint | Time | #Examined / Response | Control (0 mg/kg/day) | | 50 mg/kg/day | | 250 mg/kg/day | | 500 mg/kg/day | |
|---|---|---|---|---|---|---|---|---|---|---|
| Resistance to Removal | Baseline | # Examined | 10 | | 10 | | 10 | | 10 | |
| | | Moderate; actively avoids capture but is not aggressive | 10 | | 10 | | 10 | | 8 | |
| | | Pronounced; actively avoids capture and/or is mildly aggressive | 0 | | 0 | | 0 | | 1 | |
| | | Exaggerated; very difficult to capture and is very aggressive (i.e. tries to bite) | 0 | | 0 | | 0 | | 1 | |
| | Treated | # Examined | 10 | | 10 | | 10 | | 10 | |
| | | Moderate; actively avoids capture but is not aggressive | 10 | | 10 | | 10 | | 10 | |
| Palpebral Closure | Baseline | # Examined | 10 | | 10 | | 10 | | 10 | |
| | | Open | 10 | | 10 | | 10 | | 10 | |
| | Treated | # Examined | 10 | | 10 | | 10 | | 10 | |
| | | Open | 10 | | 10 | | 10 | | 10 | |
| Pupil Reactivity | Baseline | # Examined | 10 | | 10 | | 10 | | 10 | |
| | | Dilated, briskly reactive pupil | 10 | | 10 | | 10 | | 10 | |
| | Treated | # Examined | 10 | | 10 | | 10 | | 10 | |
| | | Dilated, briskly reactive pupil | 10 | | 10 | | 10 | | 10 | |
| Pupil Size | Baseline | # Examined | 10 | | 10 | | 10 | | 10 | |
| | | Normal pupil size | 10 | | 10 | | 10 | | 10 | |
| | Treated | # Examined | 10 | | 10 | | 10 | | 10 | |
| | | Normal pupil size | 10 | | 10 | | 10 | | 10 | |
| Lacrimation | Baseline | # Examined | 10 | | 10 | | 10 | | 10 | |
| | | Glistening cornea | 10 | | 10 | | 10 | | 10 | |
| | Treated | # Examined | 10 | | 10 | | 10 | | 10 | |
| | | Glistening cornea | 10 | | 10 | | 10 | | 10 | |

**Table 14 (continued)**
**Males**
**FOB Ranked**

| Endpoint | Time | #Examined / Response | Control (0 mg/kg/day) | | 50 mg/kg/day | | 250 mg/kg/day | | 500 mg/kg/day | |
|---|---|---|---|---|---|---|---|---|---|---|
| Salivation | Baseline | # Examined | 10 | | 10 | | 10 | | 10 | |
| | | Glistening oral cavity/lips, no wetness | 10 | | 10 | | 10 | | 10 | |
| | Treated | # Examined | 10 | | 10 | | 10 | | 10 | |
| | | Glistening oral cavity/lips, no wetness | 10 | | 10 | | 10 | | 10 | |
| Muscle Tone | Baseline | # Examined | 10 | | 10 | | 10 | | 10 | |
| | | Moderate; animal is neither very relaxed nor tense | 10 | | 10 | | 10 | | 10 | |
| | Treated | # Examined | 10 | | 10 | | 10 | | 10 | |
| | | Moderate; animal is neither very relaxed nor tense | 10 | | 10 | | 10 | | 10 | |
| Extensor Thrust | Baseline | # Examined | 10 | | 10 | | 10 | | 10 | |
| | | Moderate; clearly detectable | 10 | | 10 | | 10 | | 10 | |
| | Treated | # Examined | 10 | | 10 | | 10 | | 10 | |
| | | Moderate; clearly detectable | 9 | | 10 | | 10 | | 9 | |
| | | Pronounced; pushes vigorously | 1 | | 0 | | 0 | | 1 | |
| Reactivity to Handling | Baseline | # Examined | 10 | | 10 | | 10 | | 10 | |
| | | Moderate struggling with little or no vocalization | 10 | | 10 | | 10 | | 10 | |
| | Treated | # Examined | 10 | | 10 | | 10 | | 10 | |
| | | Moderate struggling with little or no vocalization | 10 | | 10 | | 10 | | 10 | |
| Level of Activity | Baseline | # Examined | 10 | | 10 | | 10 | | 10 | |
| | | Minimal; inactive more than 50% of the time | 0 | | 1 | | 0 | | 1 | |
| | | Moderate; inactive less than 50% of the time | 10 | | 9 | | 10 | | 9 | |
| | Treated | # Examined | 10 | | 10 | | 10 | | 10 | |
| | | Minimal; inactive more than 50% of the time | 3 | | 4 | | 3 | | 5 | |
| | | Moderate; inactive less than 50% of the time | 7 | | 6 | | 7 | | 5 | |

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**Table 14 (continued)**
**Males**
**FOB Ranked**

| Endpoint | Time | #Examined / Response | Control (0 mg/kg/day) | | 50 mg/kg/day | | 250 mg/kg/day | | 500 mg/kg/day | |
|---|---|---|---|---|---|---|---|---|---|---|
| Response to Sharp Noise | Baseline | # Examined | 10 | * | 10 | | 10 | | 10 | |
| | | Moderate; clear movement of the head, neck, ears and possibly shoulders/upper body | 10 | | 10 | | 8 | | 7 | |
| | | Pronounced; clear movement of head, neck and ears, plus clear movement of whole body. | 0 | | 0 | | 2 | | 3 | |
| | Treated | # Examined | 10 | | 10 | | 10 | | 10 | |
| | | Moderate; clear movement of the head, neck, ears and possibly shoulders/upper body | 7 | | 9 | | 8 | | 9 | |
| | | Pronounced; clear movement of head, neck and ears, plus clear movement of whole body. | 3 | | 1 | | 2 | | 0 | |
| | | Exaggerated; whole body response to stimulus more intense than "pronounced"; includes whole body going airborne | 0 | | 0 | | 0 | | 1 | |
| Response to Touch | Baseline | # Examined | 10 | | 10 | | 10 | | 10 | |
| | | Moderate; spontaneously lifts tail when touched | 10 | | 9 | | 10 | | 8 | |
| | | Pronounced; spontaneously lifts tail and acts startled | 0 | | 1 | | 0 | | 2 | |
| | Treated | # Examined | 10 | | 10 | | 10 | | 10 | |
| | | Moderate; spontaneously lifts tail when touched | 10 | | 10 | | 10 | | 9 | |
| | | Pronounced; spontaneously lifts tail and acts startled | 0 | | 0 | | 0 | | 1 | |
| Response to Tail Pinch | Baseline | # Examined | 10 | | 10 | | 10 | | 10 | |
| | | Minimal; animal flinches and may vocalize slightly | 1 | | 0 | | 0 | | 0 | |
| | | Moderate; animal flinches, moves rapidly and/or vocalizes | 9 | | 10 | | 10 | | 10 | |
| | Treated | # Examined | 10 | | 10 | | 10 | | 10 | |
| | | Minimal; animal flinches and may vocalize slightly | 2 | | 0 | | 0 | | 0 | |
| | | Moderate; animal flinches, moves rapidly and/or vocalizes | 8 | | 10 | | 10 | | 10 | |

# APPENDIX S

**Table 14 (continued)**
**Males**
**FOB Ranked**

| Endpoint | Time | #Examined / Response | Control (0 mg/kg/day) | | 50 mg/kg/day | | 250 mg/kg/day | | 500 mg/kg/day | |
|---|---|---|---|---|---|---|---|---|---|---|
| Gait Evaluation | Baseline | # Examined | 10 | | 10 | | 10 | | 10 | |
| | | Smooth and coordinated gait | 10 | | 10 | | 10 | | 10 | |
| | Treated | # Examined | 10 | | 10 | | 10 | | 10 | |
| | | Smooth and coordinated gait | 10 | | 10 | | 10 | | 10 | |
| Urination | Baseline | # Examined | 10 | | 10 | | 10 | | 10 | |
| | | No drops of urine | 3 | | 1 | | 4 | | 2 | |
| | | Minimal; a few (1-4) small drops or a small pool (~1 cm) | 3 | | 4 | | 3 | | 5 | |
| | | Moderate; a few (1-4) small pools or a moderate pool (2-3 cm) | 0 | | 2 | | 2 | | 0 | |
| | | Pronounced; a few (1-4) moderate pools or a large pool (4-5 cm) | 1 | | 1 | | 0 | | 0 | |
| | | Exaggerated; >4 moderate pools or a single pool >5 cm | 3 | | 2 | | 1 | | 3 | |
| | Treated | # Examined | 10 | | 10 | | 10 | | 10 | |
| | | No drops of urine | 1 | | 1 | | 0 | | 1 | |
| | | Minimal; a few (1-4) small drops or a small pool (~1 cm) | 3 | | 0 | | 0 | | 2 | |
| | | Moderate; a few (1-4) small pools or a moderate pool (2-3 cm) | 1 | | 1 | | 4 | | 2 | |
| | | Pronounced; a few (1-4) moderate pools or a large pool (4-5 cm) | 3 | | 1 | | 2 | | 2 | |
| | | Exaggerated; >4 moderate pools or a single pool >5 cm | 2 | | 7 | | 4 | | 3 | |

# APPENDIX S

**Table 14 (continued)**
**Males**
**FOB Ranked**

| Endpoint | Time | #Examined / Response | Control (0 mg/kg/day) | | 50 mg/kg/day | | 250 mg/kg/day | | 500 mg/kg/day | |
|---|---|---|---|---|---|---|---|---|---|---|
| Defecation | Baseline | # Examined | 10 | | 10 | | 10 | | 10 | |
| | | No pellets voided | 5 | | 7 | | 5 | | 3 | |
| | | Minimal; 1 or 2 pellets voided | 4 | | 1 | | 3 | | 5 | |
| | | Moderate; 3 pellets voided | 0 | | 1 | | 2 | | 1 | |
| | | Pronounced; 4 pellets voided | 0 | | 1 | | 0 | | 0 | |
| | | Exaggerated; 5 or more pellets voided | 1 | | 0 | | 0 | | 1 | |
| | Treated | # Examined | 10 | *** | 10 | | 10 | | 10 | * |
| | | No pellets voided | 4 | | 3 | | 1 | | 1 | |
| | | Minimal; 1 or 2 pellets voided | 3 | | 4 | | 5 | | 1 | |
| | | Moderate; 3 pellets voided | 1 | | 1 | | 3 | | 2 | |
| | | Pronounced; 4 pellets voided | 2 | | 1 | | 0 | | 3 | |
| | | Exaggerated; 5 or more pellets voided | 0 | | 1 | | 1 | | 3 | |

Asterisks indicate a significant difference across treatment groups (in the control column) or between control and a treatment group with p-values of * < 0.05, ** < 0.02 or *** < 0.01 by the Jonchkeere-Terpstra Test.

# APPENDIX S

Clinical Signs

For reproductive females and toxicology males there were statistically significant increases in the abdomen soiling and the urogenital soiling with the 500 mg/kg/day group having significantly more occurrences in more animals than did the control group (Table 15). The toxicology males also showed significantly higher urogenital soiling in the 250 mg/kg/day groups compared to control. For the toxicology female group, the soiling on the muzzle was statistically significantly difference across groups with a statistically significant increase in the 500 mg/kg/day group over that seen in the control group.

**Table 15**
**Clinical Signs**
**(number of occurrences/number of animals)**

| | Control (0 mg/kg/day) | | 50 mg/kg/day | | 250 mg/kg/day | | 500 mg/kg/day | |
|---|---|---|---|---|---|---|---|---|
| **Reproductive Females** | | | | | | | | |
| No Significant Clinical observations | 411/10 | | 439/10 | | 440/10 | | 439/10 | |
| Palpable Mass 1: Axillary, Left (small) | 2/1 | | 0/0 | | 0/0 | | 0/0 | |
| Skin, Excessive Hair Loss (minimal and moderate) | 34/2 | | 0/0 | | 0/0 | | 0/0 | |
| Skin, Scab: Muzzle, Right (focal) | 0/0 | | 0/0 | | 3/1 | | 0/0 | |
| Skin, Scab: Neck, Left or Right (focal) | 0/0 | | 4/1 | | 0/0 | | 0/0 | |
| Soiling: Abdomen, General (yellow) | 0/0 | * | 0/0 | | 3/1 | | 14/7 | *** |
| Soiling: Back, General (yellow) | 0/0 | | 0/0 | | 0/0 | | 4/1 | |
| Soiling: Nose (red) | 0/0 | | 0/0 | | 0/0 | | 1/1 | |
| Soiling: Chin (clear, red) | 0/0 | | 0/0 | | 0/0 | | 2/2 | |
| Soiling: Muzzle, General (clear, red) | 2/2 | | 0/0 | | 5/4 | | 5/3 | |
| Soiling: Urogenital, General (red, yellow) | 0/0 | *** | 1/1 | | 0/0 | | 18/6 | *** |

# APPENDIX S

| Table 15 (continued)<br>Clinical Signs<br>(number of occurrences/number of animals) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Control (0 mg/kg/day) | | 50 mg/kg/day | | 250 mg/kg/day | | 500 mg/kg/day | |
| **Toxicology Females** | | | | | | | | |
| No Significant Clinical observations | 300/10 | | 269/9 | | 286/10 | | 262/10 | |
| Soiling: Abdomen, General (yellow) | 0/0 | | 0/0 | | 6/1 | | 1/1 | |
| Soiling: Nose (red) | 0/0 | | 0/0 | | 0/0 | | 1/1 | |
| Soiling: Chin (clear, red) | 0/0 | | 1/1 | | 0/0 | | 20/3 | |
| Soiling: Muzzle, General (clear, red) | 0/0 | * | 0/0 | | 2/2 | | 7/4 | ** |
| Soiling: Urogenital, General (red, yellow) | 0/0 | | 0/0 | | 10/2 | | 2/2 | |
| Respiration, Noisy (wet) | 0/0 | | 0/0 | | 0/0 | | 7/1 | |
| Respiration, Rapid | 0/0 | | 0/0 | | 0/0 | | 5/1 | |
| | | | | | | | | |
| **Toxicology Males** | | | | | | | | |
| No Significant Clinical observations | 309/10 | | 310/10 | | 270/10 | | 227/10 | |
| Missing Tooth | 0/0 | | 0/0 | | 0/0 | | 4/1 | |
| Skin, Excessive Hair Loss (minimal and moderate) | 0/0 | | 0/0 | | 7/1 | | 0/0 | |
| Skin, Scab: Upper Back (Thoracic) (focal) | 0/0 | | 0/0 | | 6/1 | | 0/0 | |
| Soiling: Abdomen, General (yellow) | 0/0 | *** | 0/0 | | 3/2 | | 24/5 | *** |
| Soiling: Chin (clear, red) | 0/0 | | 0/0 | | 0/0 | | 1/1 | |
| Soiling: Muzzle, General (clear, red) | 1/1 | | 0/0 | | 3/3 | | 0/0 | |
| Soiling: Urogenital, General (red, yellow) | 0/0 | *** | 0/0 | | 24/5 | * | 79/10 | *** |

Asterisks indicate a significant difference across treatment groups (in the control column) or between control and a treatment group with p-values of * < 0.05, ** < 0.02 or *** < 0.01.

## Motor Activity

Collected baseline data for animal #5504, originally in the female toxicology group (50 mg/kg/day), was not used in the statistical analysis since there was not a treated motor activity counterpart. The baseline and treated untransformed motor activity data for the toxicology females (Table 16) and the toxicology males (Table 17) were homogenous and the residuals from the ANOVAs were normally distributed with the sexes combined. The repeated measures of the totals showed no time by treatment (p=0.0706) or time by treatment by sex interactions (p=0.8280). For the sexes combined, the total data showed no time by treatment interaction (p=0.0980) and the interval data did not have a significant time*treatment*interval interaction (p=0.1880) or treatment*time interaction (p=0.3799).

# APPENDIX S

**Table 16**
**Females**
**Motor Activity**

| Endpoint | Time | | Control (0 mg/kg/day) | 50 mg/kg/day | 250 mg/kg/day | 500 mg/kg/day |
|---|---|---|---|---|---|---|
| Interval 1 | Baseline | Mean | 252 | 254 | 268 | 232 |
| | | Std | 46 | 44 | 40 | 25 |
| | | N | 10 | 9 | 10 | 10 |
| | Treated | Mean | 246 | 203 | 211 | 213 |
| | | Std | 33 | 44 | 39 | 34 |
| | | N | 10 | 9 | 10 | 10 |
| Interval 2 | Baseline | Mean | 191 | 172 | 189 | 181 |
| | | Std | 41 | 30 | 46 | 22 |
| | | N | 10 | 9 | 10 | 10 |
| | Treated | Mean | 191 | 166 | 162 | 154 |
| | | Std | 62 | 44 | 42 | 30 |
| | | N | 10 | 9 | 10 | 10 |
| Interval 3 | Baseline | Mean | 156 | 105 | 131 | 137 |
| | | Std | 58 | 70 | 34 | 47 |
| | | N | 10 | 9 | 10 | 10 |
| | Treated | Mean | 150 | 122 | 146 | 127 |
| | | Std | 63 | 43 | 44 | 40 |
| | | N | 10 | 9 | 10 | 10 |
| Interval 4 | Baseline | Mean | 120 | 75 | 110 | 84 |
| | | Std | 60 | 54 | 29 | 54 |
| | | N | 10 | 9 | 10 | 10 |
| | Treated | Mean | 116 | 101 | 96 | 98 |
| | | Std | 73 | 70 | 49 | 43 |
| | | N | 10 | 9 | 10 | 10 |
| Interval 5 | Baseline | Mean | 115 | 53 | 80 | 66 |
| | | Std | 75 | 53 | 65 | 54 |
| | | N | 10 | 9 | 10 | 10 |
| | Treated | Mean | 126 | 89 | 98 | 75 |
| | | Std | 78 | 54 | 61 | 40 |
| | | N | 10 | 9 | 10 | 10 |
| Interval 6 | Baseline | Mean | 100 | 44 | 37 | 47 |
| | | Std | 65 | 44 | 72 | 58 |
| | | N | 10 | 9 | 10 | 10 |
| | Treated | Mean | 120 | 64 | 72 | 70 |
| | | Std | 115 | 44 | 51 | 35 |
| | | N | 10 | 9 | 10 | 10 |

# APPENDIX S

**Table 16 (continued)**
**Females**
**Motor Activity**

| Endpoint | Time | | Control (0 mg/kg/day) | 50 mg/kg/day | 250 mg/kg/day | 500 mg/kg/day |
|---|---|---|---|---|---|---|
| Interval 7 | Baseline | Mean | 116 | 37 | 43 | 38 |
| | | Std | 83 | 42 | 67 | 48 |
| | | N | 10 | 9 | 10 | 10 |
| | Treated | Mean | 97 | 51 | 88 | 77 |
| | | Std | 63 | 58 | 45 | 42 |
| | | N | 10 | 9 | 10 | 10 |
| Interval 8 | Baseline | Mean | 91 | 8 | 33 | 29 |
| | | Std | 50 | 21 | 38 | 47 |
| | | N | 10 | 9 | 10 | 10 |
| | Treated | Mean | 109 | 53 | 51 | 59 |
| | | Std | 64 | 52 | 35 | 37 |
| | | N | 10 | 9 | 10 | 10 |
| Interval 9 | Baseline | Mean | 66 | 17 | 65 | 19 |
| | | Std | 78 | 33 | 90 | 31 |
| | | N | 10 | 9 | 10 | 10 |
| | Treated | Mean | 83 | 52 | 62 | 74 |
| | | Std | 46 | 41 | 56 | 45 |
| | | N | 10 | 9 | 10 | 10 |
| Interval 10 | Baseline | Mean | 51 | 2 | 57 | 8 |
| | | Std | 58 | 5 | 95 | 21 |
| | | N | 10 | 9 | 10 | 10 |
| | Treated | Mean | 93 | 70 | 49 | 50 |
| | | Std | 61 | 47 | 42 | 14 |
| | | N | 10 | 9 | 10 | 10 |
| Total | Baseline | Mean | 1257 | 766 | 1013 | 840 |
| | | Std | 468 | 269 | 402 | 273 |
| | | N | 10 | 9 | 10 | 10 |
| | Treated | Mean | 1330 | 971 | 1034 | 996 |
| | | Std | 457 | 338 | 303 | 160 |
| | | N | 10 | 9 | 10 | 10 |

# APPENDIX S

**Table 17**
**Males**
**Motor Activity**

| Endpoint | Time | | Control (0 mg/kg/day) | 50 mg/kg/day | 250 mg/kg/day | 500 mg/kg/day |
|---|---|---|---|---|---|---|
| Interval 1 | Baseline | Mean | 238 | 259 | 212 | 221 |
| | | Std | 39 | 58 | 33 | 48 |
| | | N | 10 | 10 | 10 | 10 |
| | Treated | Mean | 225 | 248 | 191 | 229 |
| | | Std | 46 | 83 | 44 | 31 |
| | | N | 10 | 10 | 10 | 10 |
| Interval 2 | Baseline | Mean | 174 | 218 | 179 | 156 |
| | | Std | 54 | 55 | 46 | 49 |
| | | N | 10 | 10 | 10 | 10 |
| | Treated | Mean | 173 | 172 | 140 | 141 |
| | | Std | 57 | 65 | 56 | 34 |
| | | N | 10 | 10 | 10 | 10 |
| Interval 3 | Baseline | Mean | 141 | 151 | 131 | 115 |
| | | Std | 58 | 68 | 62 | 77 |
| | | N | 10 | 10 | 10 | 10 |
| | Treated | Mean | 91 | 134 | 102 | 100 |
| | | Std | 26 | 59 | 35 | 40 |
| | | N | 10 | 10 | 10 | 10 |
| Interval 4 | Baseline | Mean | 109 | 132 | 112 | 80 |
| | | Std | 53 | 83 | 80 | 81 |
| | | N | 10 | 10 | 10 | 10 |
| | Treated | Mean | 50 | 54 | 66 | 53 |
| | | Std | 32 | 49 | 40 | 27 |
| | | N | 10 | 10 | 10 | 10 |
| Interval 5 | Baseline | Mean | 98 | 85 | 58 | 35 |
| | | Std | 73 | 83 | 54 | 52 |
| | | N | 10 | 10 | 10 | 10 |
| | Treated | Mean | 40 | 65 | 52 | 48 |
| | | Std | 29 | 75 | 40 | 37 |
| | | N | 10 | 10 | 10 | 10 |
| Interval 6 | Baseline | Mean | 69 | 32 | 55 | 23 |
| | | Std | 67 | 46 | 58 | 40 |
| | | N | 10 | 10 | 10 | 10 |
| | Treated | Mean | 49 | 51 | 45 | 45 |
| | | Std | 41 | 51 | 37 | 55 |
| | | N | 10 | 10 | 10 | 10 |

# APPENDIX S

| Table 17 (continued) Males Motor Activity | | | | | | |
|---|---|---|---|---|---|---|
| Endpoint | Time | | Control (0 mg/kg/day) | 50 mg/kg/day | 250 mg/kg/day | 500 mg/kg/day |
| Interval 7 | Baseline | Mean | 35 | 27 | 14 | 19 |
| | | Std | 38 | 45 | 23 | 39 |
| | | N | 10 | 10 | 10 | 10 |
| | Treated | Mean | 51 | 44 | 43 | 19 |
| | | Std | 49 | 30 | 37 | 27 |
| | | N | 10 | 10 | 10 | 10 |
| Interval 8 | Baseline | Mean | 13 | 3 | 39 | 0 |
| | | Std | 31 | 9 | 48 | 1 |
| | | N | 10 | 10 | 10 | 10 |
| | Treated | Mean | 31 | 37 | 30 | 9 |
| | | Std | 34 | 35 | 35 | 21 |
| | | N | 10 | 10 | 10 | 10 |
| Interval 9 | Baseline | Mean | 15 | 3 | 34 | 1 |
| | | Std | 30 | 8 | 51 | 1 |
| | | N | 10 | 10 | 10 | 10 |
| | Treated | Mean | 26 | 45 | 22 | 6 |
| | | Std | 39 | 38 | 39 | 8 |
| | | N | 10 | 10 | 10 | 10 |
| Interval 10 | Baseline | Mean | 14 | 1 | 6 | 2 |
| | | Std | 44 | 2 | 15 | 5 |
| | | N | 10 | 10 | 10 | 10 |
| | Treated | Mean | 31 | 23 | 26 | 23 |
| | | Std | 34 | 31 | 34 | 31 |
| | | N | 10 | 10 | 10 | 10 |
| Total | Baseline | Mean | 906 | 911 | 840 | 651 |
| | | Std | 290 | 348 | 275 | 286 |
| | | N | 10 | 10 | 10 | 10 |
| | Treated | Mean | 766 | 873 | 716 | 673 |
| | | Std | 222 | 323 | 210 | 153 |
| | | N | 10 | 10 | 10 | 10 |

# APPENDIX S

Microscopic Findings

In the toxicology group females (Table 18), statistically significant trends by the Cochran-Armitage test were seen in the liver hypertrophy and liver vacuolation; hepatocellular; periportal. In the liver, Fisher's Exact tests show that the hypertrophy was significantly increased in the 250 and 500 mg/kg/day groups. For the liver valuolation, only the 500 mg/kg/day group was significantly elevated over the control group. The comparison of the graded animals only showed a significant increase in severity grade across treatment groups for liver vacuolation.

**Table 18**
**Females**
**Microscopic Findings**

| | | Control (0 mg/kg/day) | | 50 mg/kg/day | | 250 mg/kg/day | | 500 mg/kg/day | |
|---|---|---|---|---|---|---|---|---|---|
| HEART; Hyperplasia; atrium; endocardium | # Examined | 10 | | 0 | | 0 | | 10 | |
| | All Grades | 0 | | 0 | | 0 | | 1 | |
| | Mild | 0 | | 0 | | 0 | | 1 | |
| KIDNEYS; Inflammation; chronic; focal | # Examined | 10 | | 0 | | 0 | | 10 | |
| | All Grades | 3 | | 0 | | 0 | | 1 | |
| | Minimal | 3 | | 0 | | 0 | | 1 | |
| KIDNEYS; Basophilia; tubular; focal | # Examined | 10 | | 0 | | 0 | | 10 | |
| | All Grades | 3 | | 0 | | 0 | | 2 | |
| | Minimal | 3 | | 0 | | 0 | | 2 | |
| LIVER; Hypertrophy; centrilobular | # Examined | 10 | | 9 | | 10 | | 10 | |
| | All Grades | 0 | +++ | 0 | | 8 | +++ | 10 | +++ |
| | Minimal | 0 | | 0 | | 4 | | 0 | |
| | Mild | 0 | | 0 | | 4 | | 10 | |
| LIVER; Inflammation; chronic; multifocal | # Examined | 10 | | 9 | | 10 | | 10 | |
| | All Grades | 7 | | 9 | | 6 | | 4 | |
| | Minimal | 6 | | 9 | | 4 | | 4 | |
| | Mild | 1 | | 0 | | 2 | | 0 | |
| LIVER; Vacuolation; hepatocellular; periportal | # Examined | 10 | | 9 | | 10 | | 10 | |
| | All Grades | 5 | +++*** | 4 | | 7 | | 10 | ++ |
| | Minimal | 3 | | 4 | | 2 | | 0 | |
| | Mild | 2 | | 0 | | 3 | | 6 | |
| | Moderate | 0 | | 0 | | 2 | | 4 | |
| LUNGS; Hemorrhage; focal | # Examined | 10 | | 9 | | 10 | | 10 | |
| | All Grades | 0 | | 1 | | 0 | | 0 | |
| | Minimal | 0 | | 1 | | 0 | | 0 | |
| LUNGS; Hyperplasia; lymphoid tissue | # Examined | 10 | | 9 | | 10 | | 10 | |
| | All Grades | 0 | | 1 | | 1 | | 0 | |
| | Mild | 0 | | 1 | | 1 | | 0 | |
| LUNGS; Inflammation; acute; focal | # Examined | 10 | | 9 | | 10 | | 10 | |
| | All Grades | 0 | | 1 | | 0 | | 0 | |
| | Minimal | 0 | | 1 | | 0 | | 0 | |

# APPENDIX S

**Table 18 (continued)**
**Females**
**Microscopic Findings**

| | | Control (0 mg/kg/day) | | 50 mg/kg/day | | 250 mg/kg/day | | 500 mg/kg/day | |
|---|---|---|---|---|---|---|---|---|---|
| LUNGS; Inflammation; chronic; focal | # Examined | 10 | | 9 | | 10 | | 10 | |
| | All Grades | 0 | | 0 | | 1 | | 0 | |
| | Minimal | 0 | | 0 | | 1 | | 0 | |
| LUNGS; Histocytosis | # Examined | 10 | | 9 | | 10 | | 10 | |
| | All Grades | 3 | | 3 | | 2 | | 5 | |
| | Minimal | 3 | | 3 | | 1 | | 5 | |
| | Mild | 0 | | 0 | | 1 | | 0 | |
| OVARIES; Cyst; corpus luteum | # Examined | 10 | | 0 | | 0 | | 10 | |
| | Present | 1 | | 0 | | 0 | | 1 | |
| THYROID GLANDS; Cyst; ultimobranchial | # Examined | 10 | | 0 | | 0 | | 10 | |
| | Present | 2 | | 0 | | 0 | | 3 | |
| THYROID GLANDS; Ectopic Thymus | # Examined | 10 | | 0 | | 0 | | 10 | |
| | Present | 1 | | 0 | | 0 | | 0 | |
| THYROID GLANDS; Hypertrophy; follicular | # Examined | 10 | | 0 | | 0 | | 10 | |
| | All Grades | 0 | | 0 | | 0 | | 1 | |
| | Minimal | 0 | | 0 | | 0 | | 1 | |
| URINARY BLADDER; Inflammation; chronic; focal | # Examined | 10 | | 0 | | 0 | | 10 | |
| | All Grades | 0 | | 0 | | 0 | | 1 | |
| | Minimal | 0 | | 0 | | 0 | | 1 | |
| UTERUS; Inflammation; acute; diffuse | # Examined | 10 | | 0 | | 0 | | 10 | |
| | All Grades | 1 | | 0 | | 0 | | 0 | |
| | Mild | 1 | | 0 | | 0 | | 0 | |

Plus Signs indicate a significant trend by the Cochran-Armitage Test across treatment groups (in the control column) or between control and a treatment group by Fisher's Exact Test with p-values of + < 0.05, ++ < 0.02 or +++ < 0.01. Asterisks indicate a significant shift in grade across treatment groups (in the control column) with p-values of * < 0.05, ** < 0.02 or *** < 0.01.

In the toxicology group males (Table 19), statistically significant trends by the Cochran-Armitage test were seen in the liver centrilobular hypertrophy; chronic periportal inflammation in the liver, the liver hyperplasia in bile ducts associated with polyps, and the liver protoporphyrinosis. In the lungs there was an increasing trend in the histocytosis and significant trends were seen in prostate gland chronic inflammation and thyroid gland follicular hypertrophy. In the liver, Fisher's Exact tests show that the centrilobular hypertrophy was significantly increased in the 250 and 500 mg/kg/day groups over control but the periportal chronic inflammation, the hyperplasia in the bile ducts associated with protoporphyrinosis, and the protoporphyrinosis showed significant elevation over control only in the 500 mg/kg/day group. For the histocytosis in the lungs there were no pair wise significant differences between any treated group and control but there was a significant increase in severity grade across treatment groups. The 500 mg/kg/day group had a significant elevation in the incidence of chronic inflammation of

the prostate gland over that seen in the control group and there was a significant shift in grade across treatment groups as well. Both the 250 and 500 mg/kg/day groups had significantly more thyroid gland follicular hypertrophy than did the control group and the comparison of the graded animals only showed a significant increase in severity grade across treatment groups.

**Table 19**
**Toxicology Males**
**Microscopic Findings**

| | | Control (0 mg/kg/day) | | 50 mg/kg/day | | 250 mg/kg/day | | 500 mg/kg/day | |
|---|---|---|---|---|---|---|---|---|---|
| EPIDIDYMIDES; Immature; spermatid | # Examined | 10 | | 0 | | 0 | | 10 | |
| | All Grades | 0 | | 0 | | 0 | | 1 | |
| | Minimal | 0 | | 0 | | 0 | | 1 | |
| HEART; Inflammation; chronic; focal | # Examined | 10 | | 0 | | 0 | | 10 | |
| | All Grades | 1 | | 0 | | 0 | | 1 | |
| | Minimal | 1 | | 0 | | 0 | | 1 | |
| KIDNEYS; Hyperplasia; tubular; focal | # Examined | 10 | | 0 | | 0 | | 10 | |
| | All Grades | 0 | | 0 | | 0 | | 1 | |
| | Moderate | 0 | | 0 | | 0 | | 1 | |
| KIDNEYS; Infarction; focal | # Examined | 10 | | 0 | | 0 | | 10 | |
| | All Grades | 0 | | 0 | | 0 | | 1 | |
| | Moderate | 0 | | 0 | | 0 | | 1 | |
| KIDNEYS; Inflammation; chronic; focal | # Examined | 10 | | 0 | | 0 | | 10 | |
| | All Grades | 3 | | 0 | | 0 | | 1 | |
| | Mild | 3 | | 0 | | 0 | | 1 | |
| KIDNEYS; Basophilia; tubular; focal | # Examined | 10 | | 0 | | 0 | | 10 | |
| | All Grades | 4 | | 0 | | 0 | | 5 | |
| | Minimal | 3 | | 0 | | 0 | | 4 | |
| | Mild | 1 | | 0 | | 0 | | 1 | |
| LIVER; Hypertrophy; centrilobular | # Examined | 10 | | 10 | | 10 | | 10 | |
| | All Grades | 0 | +++ | 1 | | 8 | +++ | 8 | +++ |
| | Minimal | 0 | | 1 | | 7 | | 3 | |
| | Mild | 0 | | 0 | | 1 | | 5 | |
| LIVER; Inflammation; chronic; multifocal | # Examined | 10 | | 10 | | 10 | | 10 | |
| | All Grades | 9 | | 8 | | 8 | | 1 | |
| | Minimal | 8 | | 7 | | 8 | | 1 | |
| | Mild | 1 | | 1 | | 0 | | 0 | |
| LIVER; Inflammation; chronic; periportal | # Examined | 10 | | 10 | | 10 | | 10 | |
| | All Grades | 0 | +++ | 0 | | 0 | | 9 | +++ |
| | Minimal | 0 | | 0 | | 0 | | 4 | |
| | Mild | 0 | | 0 | | 0 | | 5 | |

# APPENDIX S

**Table 19 (continued)**
**Toxicology Males**
**Microscopic Findings**

| | | Control (0 mg/kg/day) | | 50 mg/kg/day | | 250 mg/kg/day | | 500 mg/kg/day | |
|---|---|---|---|---|---|---|---|---|---|
| LIVER; Hyperplasia, Bile Duct, Assoc W Pps | # Examined | 10 | | 10 | | 10 | | 10 | |
| | All Grades | 0 | +++ | 0 | | 0 | | 8 | +++ |
| | Minimal | 0 | | 0 | | 0 | | 3 | |
| | Mild | 0 | | 0 | | 0 | | 3 | |
| | Moderate | 0 | | 0 | | 0 | | 2 | |
| LIVER; Vacuolation; hepatocellular; centrilobular | # Examined | 10 | | 10 | | 10 | | 10 | |
| | All Grades | 0 | | 1 | | 0 | | 0 | |
| | Mild | 0 | | 1 | | 0 | | 0 | |
| LIVER; Vacuolation; hepatocellular; periportal | # Examined | 10 | | 10 | | 10 | | 10 | |
| | All Grades | 2 | | 0 | | 2 | | 3 | |
| | Minimal | 1 | | 0 | | 1 | | 0 | |
| | Mild | 1 | | 0 | | 1 | | 3 | |
| LIVER; Protoporphyrinosis | # Examined | 10 | | 10 | | 10 | | 10 | |
| | All Grades | 0 | +++ | 0 | | 0 | | 9 | +++ |
| | Minimal | 0 | | 0 | | 0 | | 5 | |
| | Mild | 0 | | 0 | | 0 | | 1 | |
| | Moderate | 0 | | 0 | | 0 | | 3 | |
| LUNGS; Hemorrhage; focal | # Examined | 10 | | 10 | | 10 | | 10 | |
| | All Grades | 2 | | 0 | | 1 | | 1 | |
| | Minimal | 2 | | 0 | | 1 | | 1 | |
| LUNGS; Hyperplasia; lymphoid tissue | # Examined | 10 | | 10 | | 10 | | 10 | |
| | All Grades | 0 | | 1 | | 1 | | 0 | |
| | Mild | 0 | | 1 | | 1 | | 0 | |
| LUNGS; Inflammation; acute; focal | # Examined | 10 | | 10 | | 10 | | 10 | |
| | All Grades | 1 | | 0 | | 0 | | 0 | |
| | Minimal | 1 | | 0 | | 0 | | 0 | |
| LUNGS; Inflammation; chronic; focal | # Examined | 10 | | 10 | | 10 | | 10 | |
| | All Grades | 1 | | 0 | | 0 | | 0 | |
| | Minimal | 1 | | 0 | | 0 | | 0 | |
| LUNGS; Inflammation; chronic; multifocal | # Examined | 10 | | 10 | | 10 | | 10 | |
| | All Grades | 1 | | 0 | | 0 | | 1 | |
| | Minimal | 1 | | 0 | | 0 | | 1 | |
| LUNGS; Histocytosis | # Examined | 10 | | 10 | | 10 | | 10 | |
| | All Grades | 4 | ++* | 4 | | 8 | | 8 | |
| | Minimal | 4 | | 4 | | 4 | | 8 | |
| | Mild | 0 | | 0 | | 4 | | 0 | |

# APPENDIX S

**Table 19 (continued)**
**Toxicology Males**
**Microscopic Findings**

| | | Control (0 mg/kg/day) | | 50 mg/kg/day | | 250 mg/kg/day | | 500 mg/kg/day | |
|---|---|---|---|---|---|---|---|---|---|
| PROSTATE GLAND; Inflammation; chronic | # Examined | 10 | | 10 | | 10 | | 10 | |
| | All Grades | 2 | +* | 6 | | 5 | | 7 | + |
| | Minimal | 0 | | 3 | | 5 | | 1 | |
| | Mild | 1 | | 2 | | 0 | | 6 | |
| | Moderate | 1 | | 1 | | 0 | | 0 | |
| PROSTATE GLAND; Inflammation; chronic-active | # Examined | 10 | | 10 | | 10 | | 10 | |
| | All Grades | 0 | | 1 | | 0 | | 0 | |
| | Marked | 0 | | 1 | | 0 | | 0 | |
| PROSTATE GLAND; Necrosis; single cell | # Examined | 10 | | 10 | | 10 | | 10 | |
| | All Grades | 1 | | 0 | | 0 | | 1 | |
| | Minimal | 1 | | 0 | | 0 | | 1 | |
| SEMINAL VESICLES; Atrophy; unilateral | # Examined | 10 | | 0 | | 0 | | 10 | |
| | All Grades | 0 | | 0 | | 0 | | 1 | |
| | Mild | 0 | | 0 | | 0 | | 1 | |
| TESTES; Degeneration; spermatid | # Examined | 10 | | 0 | | 0 | | 10 | |
| | All Grades | 0 | | 0 | | 0 | | 1 | |
| | Minimal | 0 | | 0 | | 0 | | 1 | |
| TESTES; Cyst; seminiferous tubule | # Examined | 10 | | 0 | | 0 | | 10 | |
| | Present | 0 | | 0 | | 0 | | 1 | |
| THYROID GLANDS; Cyst; ultimobranchial | # Examined | 10 | | 10 | | 10 | | 10 | |
| | Present | 2 | | 3 | | 0 | | 1 | |
| THYROID GLANDS; Ectopic Thymus | # Examined | 10 | | 10 | | 10 | | 10 | |
| | Present | 1 | | 0 | | 0 | | 0 | |
| THYROID GLANDS; Hypertrophy; follicular | # Examined | 10 | | 10 | | 10 | | 10 | |
| | All Grades | 1 | +++* | 0 | | 8 | +++ | 9 | +++ |
| | Minimal | 1 | | 0 | | 5 | | 1 | |
| | Mild | 0 | | 0 | | 3 | | 8 | |

Plus Signs indicate a significant trend by the Cochran-Armitage Test across treatment groups (in the control column) or between control and a treatment group by Fisher's Exact Test with p-values of + < 0.05, ++ < 0.02 or +++ < 0.01. Asterisks indicate a significant shift in grade across treatment groups (in the control column) with p-values of * < 0.05, ** < 0.02 or *** < 0.01.

# APPENDIX S

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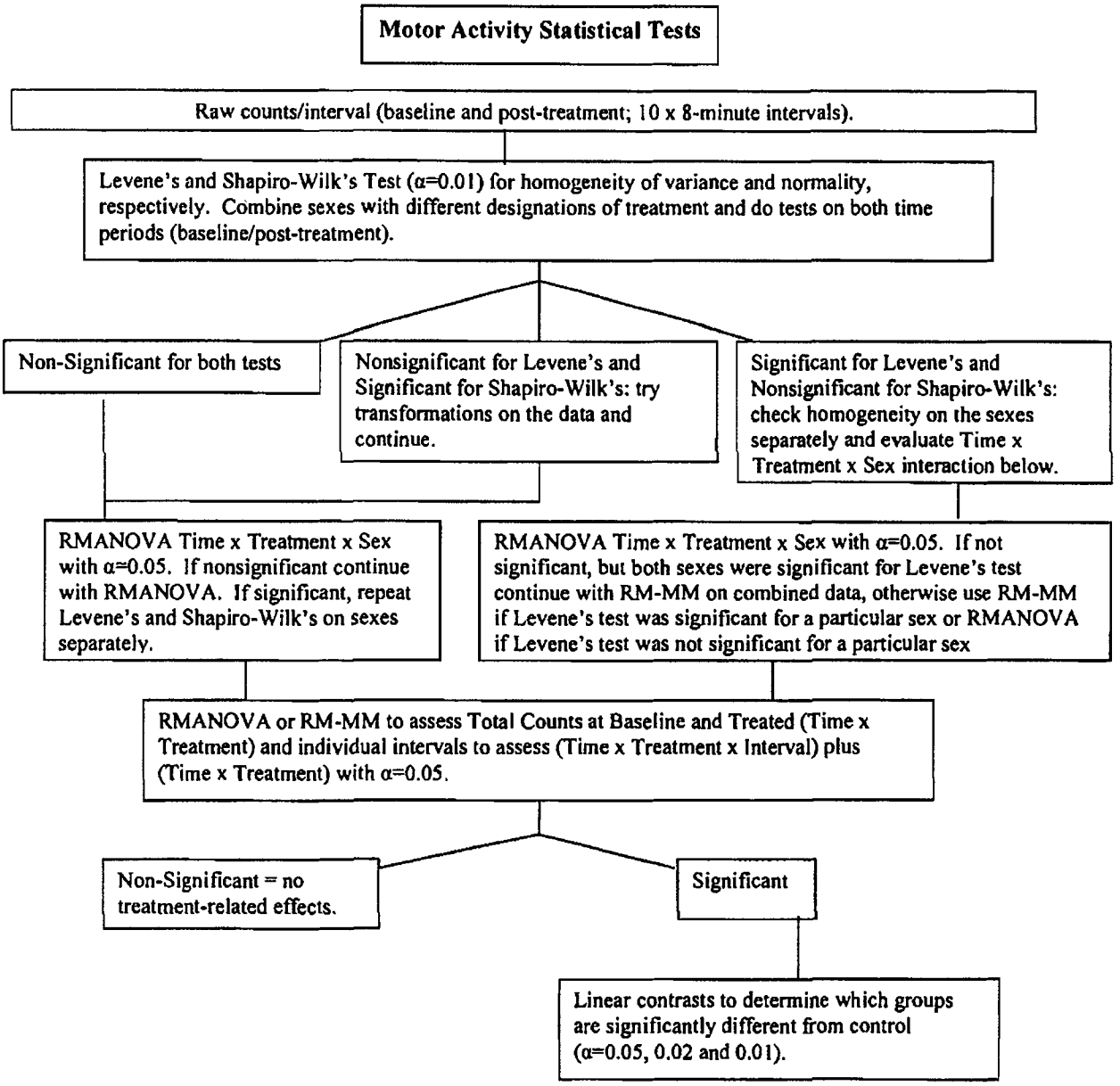
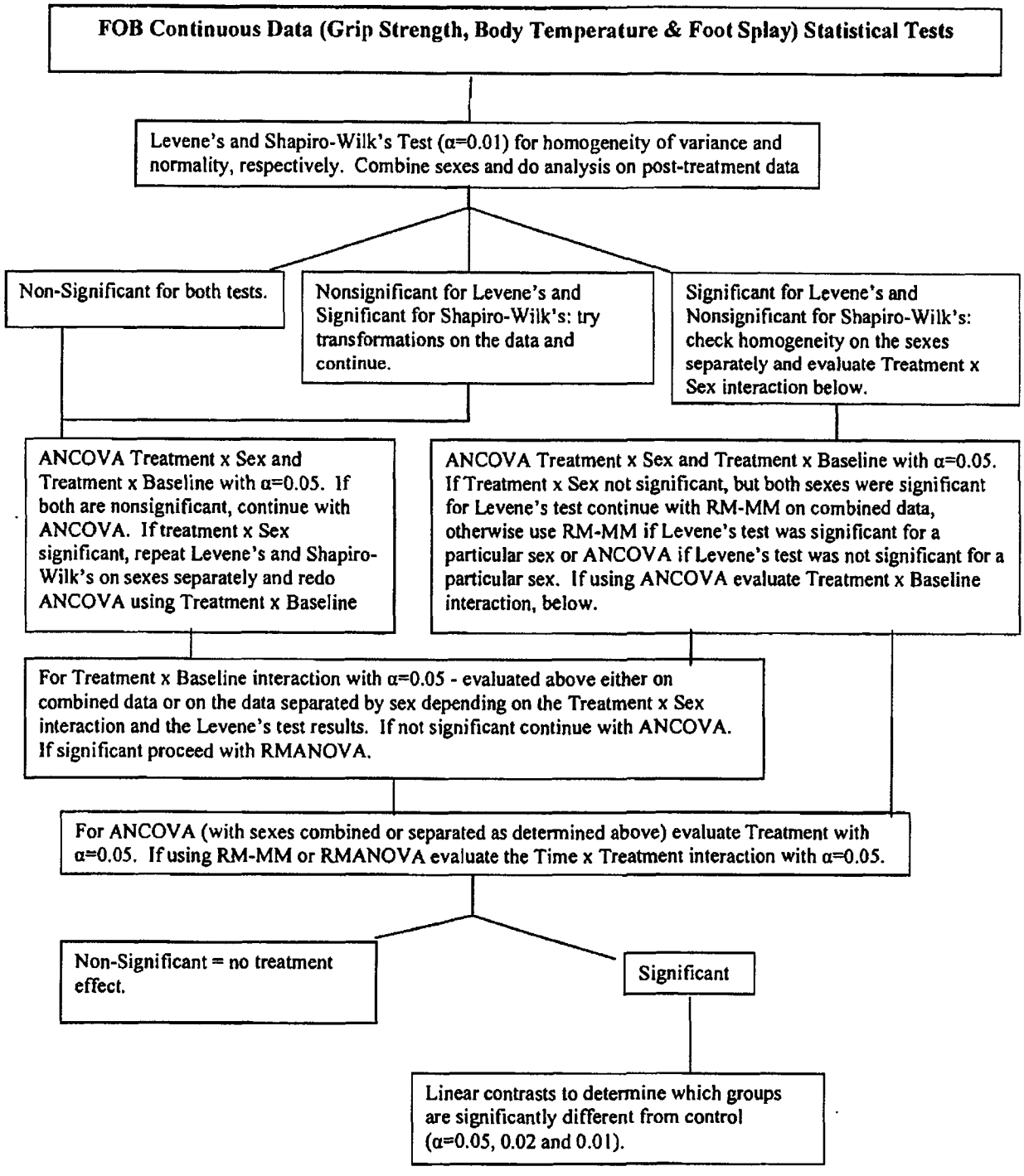
# APPENDIX S



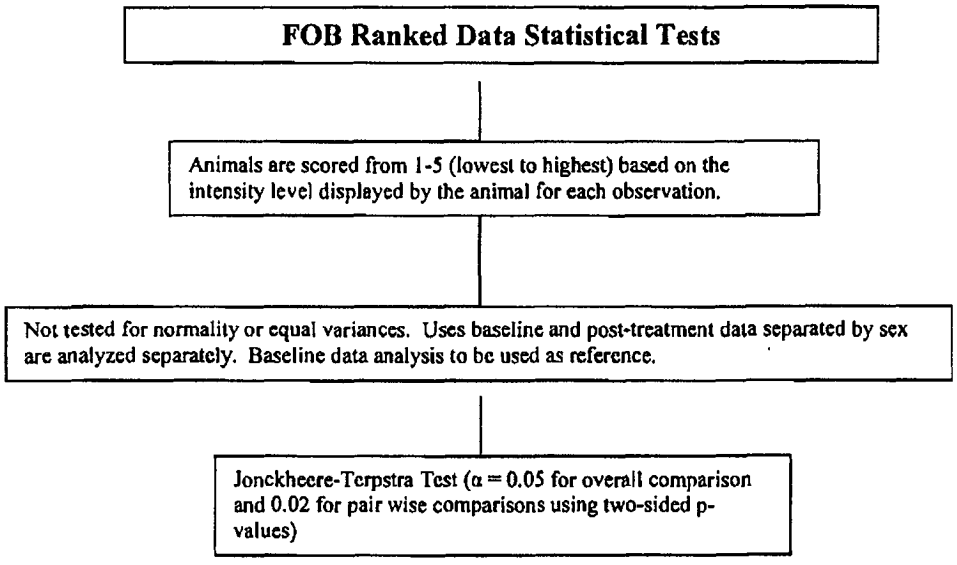

Note: RM-MM = Repeated Measures Mixed Modeling; RMANOVA = Repeated Measures Analysis of Variance. The p-value given for the Type III SS is used for RM-MM and Pillia's Trace is used for RMANOVA.

# APPENDIX S




Note: ANCOVA = Analysis of Covariance; RM-MM = Repeated Measures Mixed Modeling; RMANOVA = Repeated Measures Analysis of Variance. The p-value given for the Type III SS is used for ANCOVA and RM-MM and Pillia's Trace is used for RMANOVA.

# APPENDIX S


FOB Ranked Data Statistical Tests
Animals are scored from 1-5 (lowest to highest) based on the intensity level displayed by the animal for each observation.
Not tested for normality or equal variances. Uses baseline and post-treatment data separated by sex are analyzed separately. Baseline data analysis to be used as reference.
Jonckheere-Terpstra Test (α = 0.05 for overall comparison and 0.02 for pair wise comparisons using two-sided p-values)

APPENDIX T
**DOW CORNING CORPORATION**
**HEALTH & ENVIRONMENTAL SCIENCES**
**TECHNICAL REPORT**

| | |
|---|---|
| Title: | Characterization of Dimethylsilanediol (Reference Number 21436-84) |
| HES Study Number: | 10871-102 |
| Test Article: | Dimethylsilanediol |
| Study Director: | Debra Stutts |
| Sponsor: | Silicones Environmental, Health and Safety Council (SEHSC)<br>2325 Dulles Corner Boulevard, Suite 500<br>Herndon, VA 20171 |
| HES Group Manager: | Roy A. Campbell<br>Health and Environmental Sciences (HES)<br>Chemistry and Environmental |
| Testing Facility: | Health and Environmental Sciences<br>Dow Corning Corporation<br>2200 W. Salzburg Road<br>Auburn, MI 48611 |
| Study Completion Date: | 7 August 2008 |

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## ABSTRACT

Dimethylsilanediol (Reference Number 21436-84, (supplied as Dow Corning ® XX-1240 Dev Sample) was characterized according to EPA (TSCA) Good Laboratory Practices 40 CFR Part 792. Characterization included physical description, area percent purity by GC/FID and confirmation of identity by GC-MS.

The physical appearance of the test article was observed to be a white solid. The GC/FID area percent purity for dimethylsilanediol was 97.8 ± 0.01 based on the average of 3 replicate injections. GC-MS supports the identification of the test article as dimethylsilanediol. This test article meets the specification for physical description and identification as defined in the Material Safety Data Sheet (MSDS).

## GLP COMPLIANCE STATEMENT

This study was conducted in accordance with EPA (TSCA) Good Laboratory Practices 40 CFR Part 792.

Debra Stutts, B. S.
Associate Analytical Specialist
Study Director

7 Aug 2008
Date

Roy A. Campbell, B. S.
Health and Environmental Sciences (HES)
Manager-Chemistry and Environmental

07/Aug/2008
Date

# QUALITY ASSURANCE STATEMENT

Title: Characterization of Dimethylsilanediol
(Reference Number 21436-84)

Study Number: 10871-102

This study has been audited by the Dow Corning Corporation Health and Environmental Sciences Quality Assurance Unit according to approved Standard Operating Procedures to assure that the raw data are accurately reflected within this final report. The following are the inspection dates and the dates inspection findings were reported.

| Dates of Inspection | Phase Inspected | Findings Reported to Study Director and Management |
|---|---|---|
| 11 Jun 08 | Draft Protocol Review | 12 Jun 08 |
| 17 Jun 08 | Physical Description | 17 Jun 08 |
| 25-28 Jul 08 | Draft Final Report and Associated Raw Data Review | 28 Jul 08 |

Nancy C Price

Nancy C. Price, M.S., MPH
Associate Quality Assurance Specialist
Dow Corning Corporation
Health & Environmental Sciences

06 Aug 08
Date

## APPROVAL SIGNATURES

This report consists of pages 1 through 14.

Debra Stutts, B. S.
Associate Analytical Specialist
Study Director

7 Aug 2008
Date

Roy A. Campbell, B. S.
Health and Environmental Sciences (HES)
Manager-Chemistry and Environmental

07/Aug/2008
Date

## STUDY INFORMATION

| | |
|---|---|
| Study Initiation Date: | 13 June 2008 |
| Experimental Start Date: | 17 June 2008 |
| Experimental Termination Date: | 17 June 2008 |
| Study Completion Date: | 7 August 2008 |

**A. Study Purpose**

The objective of this study was to characterize the test article, dimethylsilanediol.

**B. Test Article / Substance / Item**

**Identification:** Dimethylsilanediol (Supplied as Dow Corning ® XX-1240 Dev Sample)
**Reference Number:** 21436-84
**Expiration Date:** 15 August 2008
**Source:** Dow Corning Corporation, Auburn, Michigan 48611
**CAS Number:** 1066-42-8
**Physical Description:** White solid, refer to MSDS
**Stability:** Stable, if stored at -20 to -80°C over desiccant, according to the information provided by sample submitter
**Purity:** 97.8 ± 0.01 area % purity, as determined by this study
**Solubility:** Water, ethanol, refer to information provided by sample submitter, may be soluble in other common organic solvents
**Storage Conditions:** Store at -20°C to -80°C over desiccant, according to the information provided by sample submitter
**Archive:** A reserve sample was not retained for this study.

**C. Labeling**

The original test article container for this study was labeled with the following information: study number, name of test article, reference number, container accession number, concentration, storage conditions, expiration date, initials of the individual distributing the test article and date the test article was dispensed into the container.

**D. Route of Exposure and Justification**

As the test article is the test system, this is not applicable.

**E. Experimental Procedures**

1. **Physical Description**

   The physical appearance of the test article was determined by visual examination.

2. **GC/FID**

   A 0.02 g aliquot of dimethylsilanediol was dissolved in 1.5 mL acetone in an autosampler vial. A Hewlett Packard (HP) 6890 GC with flame ionization detector (FID) and HP 7673 autosampler was used to determine an area percent purity of dimethylsilandiol, based on the average of 3 replicate injections (1.0 µL). A solvent blank (acetone) was injected (1µL injection volume) prior to the test article solution analysis. The actual instrument parameters are shown in Table I. The GC area percent results were calculated as the ratio of dimethylsilanediol peak area divided by the sum of all peak areas. The GC/FID performance was verified by conducting triplicate 1 µL injections of an Agilent checkout sample using the autosampler. Hewlett Packard Chemstation revision B.03.01-SR1 software was used for data acquisition and analysis. Prior to analyzing dimethylsilanediol, the oven temperature was increased to 280 °C for 95 minutes to prevent carry over by heating the column to burn off any residual material left from previous analyses. Once a stable baseline was observed, the GC performance was considered acceptable for use.

**Table I. GC/FID Instrument Parameters**

| Parameter | Setting |
|---|---|
| Oven Temperature Program | 50 °C (hold 3 min) to 250°C at 25°C/min (hold 5 min) |
| Inlet Temperature | 150 °C |
| Detector Temperature | 280 °C |
| Capillary Column | DB-5, 0.32 mm inner diameter 30 m length, 0.25 µm film thickness |
| Mode | Constant flow, He carrier |
| Initial Flow | 1.1 mL/min |
| Split Ratio | 65:1 |

3. **GC-MS Analysis**

A 0.02 g aliquot of dimethylsilanediol was dissolved in 1.5 mL acetone in an autosampler vial. An HP 5890A Series II GC with an HP 5970B mass selective detector (MSD) was used to verify the identity of the major component in the test article solution as dimethylsilanediol by manual injection (~0.2 µL). HP ChemStation version B.02.05 software and HP MS ChemStation version C.03.00 software were used for data acquisition and analysis. The standard autotune procedure was conducted prior to analyzing the test article. The standard autotune is an automated tuning program that uses perfluorotributylamine (PFTBA) to optimize the MS for general-purpose electron impact ionization (EI) operation. The GC oven temperature was increased to 280 °C for 30 min to prevent carry over by burning off residual material remaining from previous analyses. An acetone solvent blank was injected (~0.2 µL) prior to the test article solution analysis. The actual instrument parameters used are shown in Table II.

**Table II. GC-MS Instrument Parameters**

| Parameter | Setting |
|---|---|
| Oven Temperature Program | 40 °C (hold 2 min) to 80 °C at 20 °C/min (hold 6 min) |
| Inlet Temperature | 250 °C |
| Capillary Column | HP-5MS (5%-phenylmethylsilicone), 0.25 mm inner diameter, 30 m length, 0.25 µm film thickness |
| Mode | Constant flow, He carrier 7.3 psi at 70 °C, vacuum compensation on |
| Split Ratio | 200:1 |
| Mass Scan Range | 30-500 atomic mass units |

**F. Data Analysis**

Calculation of average and standard deviation for determination of area percent purity by GC/FID was performed.

**G. Deviations**

There were no circumstances that affected the quality or integrity of the data.

## H. Results and Discussion

### 1. Physical Description

The physical appearance of the test article was observed to be a white solid, which is consistent with the physical form and color in the MSDS.

### 2. GC/FID Analysis

The GC/FID area percent purity for dimethylsilanediol was 97.8 ± 0.01 based on the average of 3 replicate injections. The results are summarized in Table III. The peak area of the major peak (DMSD) was split during integration. The peaks areas were summed to obtain the total peak area for DMSD. A representative GC/FID chromatogram of the test article is shown in Figure 2. The GC/FID performance verification passed the acceptance criteria.

### 3. GC-MS Analysis

The major peak in the total ion chromatogram (TIC) eluted at a retention time of 2.54 minutes and is shown in Figure 3. A small molecular ion (m/z 92) is present in the mass spectrum shown in Figure 4. The base peak (m/z 77) corresponds to $CH_3Si(OH)_2^+$ and is formed by the loss of a methyl group from the parent molecule (M = 92). The fragmentation pattern is consistent with that expected for dimethylsilanediol. The mass spectrum for the major component in the total ion chromatogram (TIC) for the test article analysis was library searched and a reasonable match for dimethylsilanediol was not obtained.

## I. Conclusions

Dimethylsilanediol was characterized according to EPA (TSCA) Good Laboratory Practices 40 CFR Part 792. The physical appearance of the test article was observed to be a white solid. The GC/FID area percent purity for dimethylsilanediol was 97.8 ± 0.01 based on the average of 3 replicate injections. GC-MS supports the identification of the test article as dimethylsilanediol. This test article meets the specification for physical description and identification as defined in the Material Safety Data Sheet (MSDS).

## J. Archive

Protocol, study authorization documentation, raw data, correspondence and final report (at minimum) will be retained for five (5) years in the HES Archives, Dow Corning Corporation, 2200 W. Salzburg Road, Auburn, MI 48611. Thereafter, the Sponsor will be contacted for the disposition of the archived material. The Sponsor will then assume responsibility for the archived materials and any expense for further archiving, disposal, and/or shipment.

## K. References

1. Moore, J. A. In The Analytical Chemistry of Silicones: A. L. Smith, ed.; Mass Spectrometry, Volume 112, Chapter 13; John Wiley & Sons, Inc.; New York, NY; 1991.
2. Material Safety Data Sheet

**Table III. GC/FID Purity Results for Dimethylsilanediol**

| Replicate | Peak # | Retention Time (min) | Area % | Peak Assignment |
|---|---|---|---|---|
| 1 | 1 | 2.709 | -- | Impurity in Acetone |
| | 2 | 2.879 | -- | Acetone |
| | 3 | 4.046 | 97.9 | DMSD |
| | 4 | 6.262 | 1.9 | Impurity in DMSD |
| | 5 | 7.662 | 0.2 | Impurity in DMSD |
| | | | | |
| 2 | 1 | 2.708 | -- | Impurity in Acetone |
| | 2 | 2.879 | -- | Acetone |
| | 3 | 4.047 | 97.7 | DMSD |
| | 4 | 6.263 | 2.1 | Impurity in DMSD |
| | 5 | 7.662 | 0.2 | Impurity in DMSD |
| | | | | |
| 3 | 1 | 2.713 | -- | Impurity in Acetone |
| | 2 | 2.879 | -- | Acetone |
| | 3 | 4.049 | 97.8 | DMSD |
| | 4 | 6.262 | 2.0 | Impurity in DMSD |
| | 5 | 7.661 | 0.2 | Impurity in DMSD |
| | | | 97.8 | AREA % PURITY DMSD |
| | | | | |
| | | Mean (n=3) | 97.8 | MEAN AREA % PURITY DMSD |
| | | Standard Deviation | 0.01 | |
| | | RSD (%) | 0.01 | |

* Area attributable to acetone, not included in purity calculations

$$\text{Area \%} = \frac{\text{Area of component peak}}{\text{(Total area from integration -- area attributable to solvent)}} * 100\%$$

Figure 1. GC/FID Chromatogram of Acetone

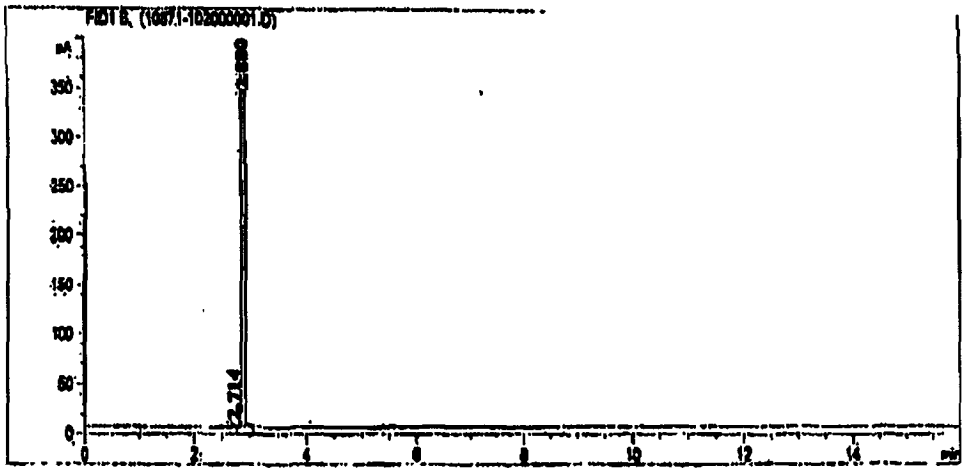


Figure 2. GC/FID Chromatogram of Dimethylsilanediol in Acetone

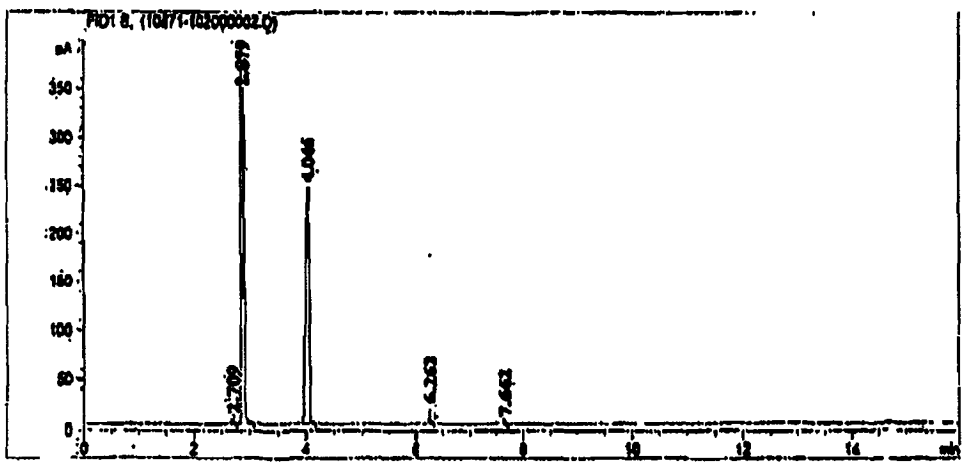


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Figure 3. Total Ion Chromatogram from GC-MS Analysis of Dimethylsilanediol in Acetone

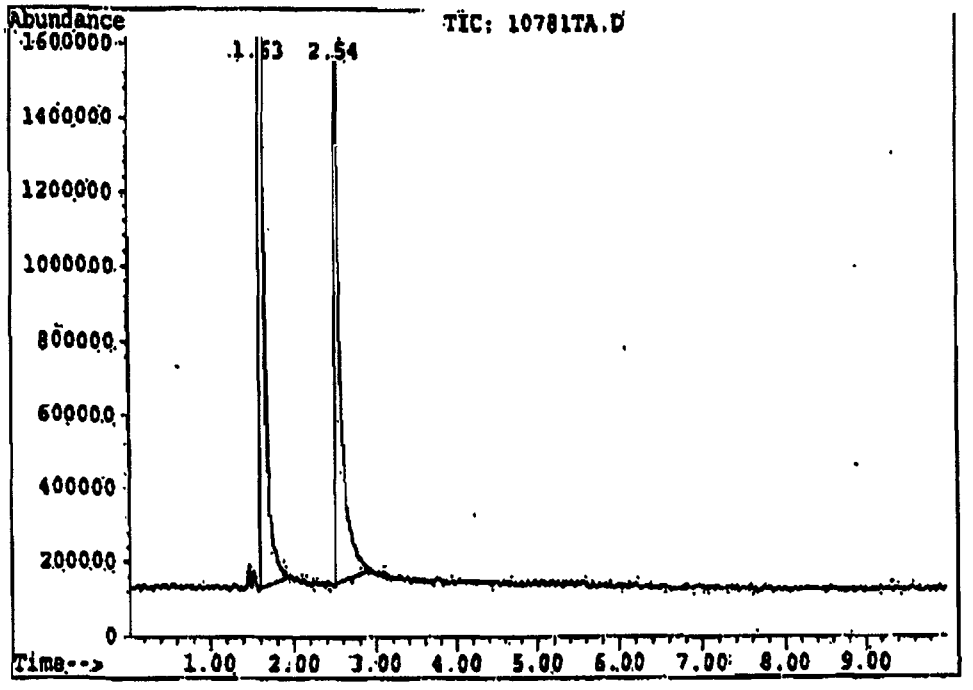
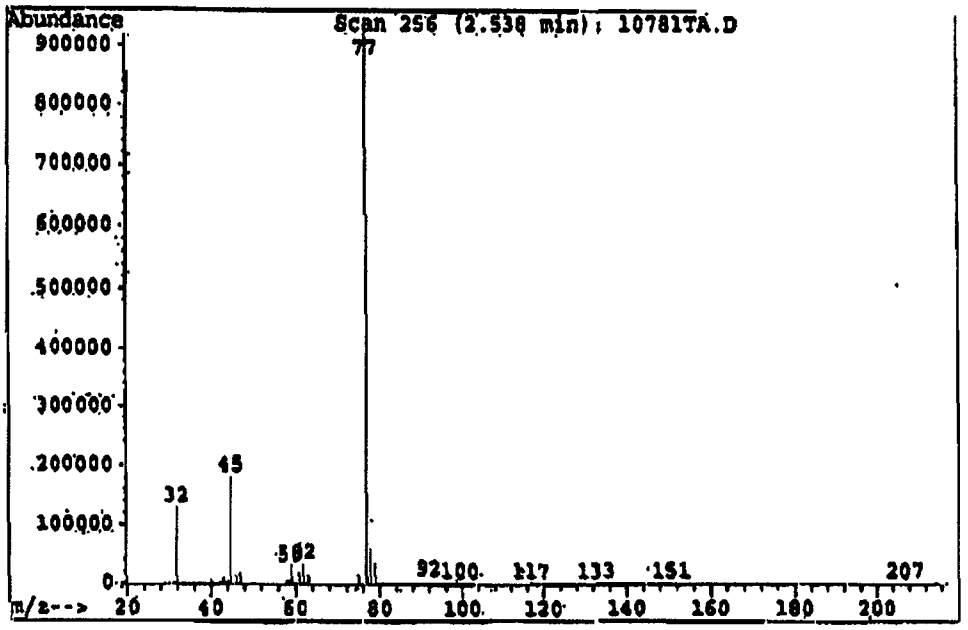


Figure 4. Mass Spectrum of Dimethylsilanediol



**Appendix U**

# DOW CORNING CORPORATION
# HEALTH & ENVIRONMENTAL SCIENCES

## CONTRIBUTING SCIENTIST REPORT

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| | |
|---|---|
| **Report Title:** | Concentration, Homogeneity and Stability Verification of Dimethylsilanediol in Corn Oil |
| **HES Study Number:** | 10872-102 |
| **Test Article:** | Dimethylsilanediol (DMSD) |
| **Contributing Scientist:** | Debra Stutts, B.S. |
| **Sponsor:** | Silicones Environmental, Health and Safety Council<br>2325 Dulles Corner Boulevard, Suite 500<br>Herndon, VA 20171 |
| **HES Group Manager:** | Roy A. Campbell, B. S.<br>Health and Environmental Sciences (HES)<br>Chemistry and Environmental |
| **Testing Facility:** | Dow Corning Corporation<br>Health and Environmental Sciences<br>2200 West Salzburg Road<br>Auburn, Michigan 48611 |
| **Analysis Start Date:** | 19 June 2008 |
| **Analysis End Date:** | 30 June 2008 |

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## APPROVAL SIGNATURES

Approved by: Debra Stutts 14 July 2009
Debra Stutts, B.S.
Associate Analytical Specialist

Roy A Campbell 14-July-2009
Roy A. Campbell, B.S.
Manager-Chemistry and Environmental

## OBJECTIVE

This document describes the results from a GC method for verifying the concentration, homogeneity and stability of dimethylsilanediol (DMSD) in corn oil.

## EXPERIMENTAL

***Analysis of 11, 55 and 110 mg/g dose solutions and control***

**Preparation of Standards:**

Standards of DMSD (supplied as Dow Corning ® XX-1240 Dev Sample, reference 21436-84, expiration date 08/15/08, purity 97.8%, CAS Number 1066-42-8) in acetone were prepared by diluting a weighed amount of DMSD with acetone in a volumetric flask to obtain a standard stock solution. Aliquots of the stock solution were further diluted with acetone to obtain a set of solvent standards. The preparation of each set of standards was documented in the study file. An aliquot of each solvent standard was placed in an autosampler vial and analyzed.

**Preparation of Corn Oil Samples for Analysis:**

The suspensions of DMSD in corn oil were obtained in 100 mL septum sealed glass serum vials. The suspensions were mixed well by rotating the inverted serum vial. Aliquots (approximately 100 mg to 1 gram, depending on the dose level) of the suspension were removed from the inverted serum vial using a 13 gauge needle affixed to a 1 mL syringe and transferred into tared volumetric flasks. For homogeneity sampling of the 11 and 110 mg/g dose solutions, a total of three aliquots were taken from the vial from three locations within the inverted container. The aliquots were diluted to volume with acetone and the solution was mixed well. The aliquots were transferred to autosampler vials and analyzed by GC/FID using the following conditions.

**GC-FID System Components used for Analyses:**

Hewlett Packard 6890 GC-FID SN US00001792 Model G1530A
GC Software: HP Chemstation Revision B.03.01-SR1
Microsoft Windows XP Professional
HP 7683B Autosampler
Injector G2913A SN CN54829433
Controller G2912A SN CN54800315
Sample Tray G2614A SN CN54737451

**Run Parameters**

1.0µL injection, Splitless
Injection Port: 200°C
    Pressure: 12.67 psi
    Total Flow: 65.5 mL/min
    Gas Type: Helium
Oven: Initial Temp: 50°C
    Initial Time: 2 min
    Ramp 20°C/min to 200°C
    Column: HP-5 5% Phenyl Methyl Siloxane 30m x 320µm x 1.00µm

Constant Pressure
Detector Temperature: 280°C
Hydrogen Flow 40.0 mL/min
Air Flow: 400 mL/min
Makeup Gas: Helium
Combined Flow: 25.0 mL/min

**DATA ANALYSIS**

A set of solvent standards, comprised of four concentrations, was used to establish a calibration curve for the test article. Trend lines and their mathematical equations were generated by linear regression analysis of the solvent standard data (mean peak area) using Microsoft Excel ® 2003. Verification of the test article concentration in corn oil was performed by comparing the target concentration of the test substance to the mean observed test substance concentration by refitting the peak areas to the standard curve.

Statistical methods including mean, standard deviation, relative standard deviation and linear regression analyses were performed.

**DEVIATIONS**

There were no circumstances that may have adversely affected the quality or integrity of the data.

**RESULTS AND DISCUSSION**

The results of the concentration and homogeneity verification for DMSD are summarized in Table I. The initial concentration verification was conducted on corn oil suspensions mixed 19 June 2008 (mix 2). The mean observed concentration of the analyte was determined to be 10.3, 49.8 and 103 mg/g for the dosing solutions as compared to nominal concentrations of 11, 55 and 110 mg/g, respectively. The relative standard deviation between the samples from 3 locations at the low and high dose levels was 0.9 and 1.4%, respectively; therefore, the suspensions were determined to be homogeneous. The low and high dose levels were reanalyzed after 11 days; the observed concentrations were 9.76 and 102 mg/g, 94 and 99% of the observed concentration on the day of mixing.

**CONCLUSIONS**

The mean observed concentrations for the 11, 55 and 110 mg/g dosing suspensions were determined to be 10.3, 49.8 and 103 mg/g, respectively. The suspensions were homogeneous at the low and high dose levels. The suspensions were found to be stable for at least 11 days.

TABLES

**Table I - Homogeneity and Concentration Verification**
Mix 2 on 19 June 2008

| Dose Level | Nominal Conc. (mg/g) | Aliquot ID | Observed Concentration (mg/g) | Mean Observed Concentration (mg/g) [b] | Standard Deviation | Percent Relative Standard Deviation | Percent of Nominal |
|---|---|---|---|---|---|---|---|
| **0** | | Control Corn Oil | N.D [a] | N.D | --- | --- | |
| **Low** | 11 | Top | 10.2 | 10.3 | 0.09 | 0.9 | 94 |
| | | Middle | 10.4 | | | | |
| | | Bottom | 10.4 | | | | |
| **Middle** | 55 | 1 | 49.9 | 49.8 | 6.38 | 5.2 | 91 |
| | | 2 | 47.2 | | | | |
| | | 3 | 52.4 | | | | |
| **High** | 110 | Top | 104 | 103 | 1.45 | 1.4 | 94 |
| | | Middle | 101 | | | | |
| | | Bottom | 104 | | | | |

[a]ND = not detected, Limit of Detection (LOD) < 0.41 mg/g
[b]determined from the mean of the mean observed concentration, n = 3

**Table II - Stability Verification**
Mix 2 on 19 June 2008
Date of Analysis 30 June1008

| Dose Level (mg/kg/day) | Nominal Conc. (mg/g) | Mean Observed Concentration 19 June 2008 (mg/g) [a] | Mean Observed Concentration 30 June 2008 (mg/g) [a] | Percent of 19 June 2008 Concentration |
|---|---|---|---|---|
| **Low** | 11 | 10.3 | 9.76 | 94 |
| **High** | 110 | 103 | 102 | 99 |

[a]determined from the mean of the mean observed concentration, n = 3

Figure 1 – GC/FID Chromatogram of Control Corn Oil in Acetone

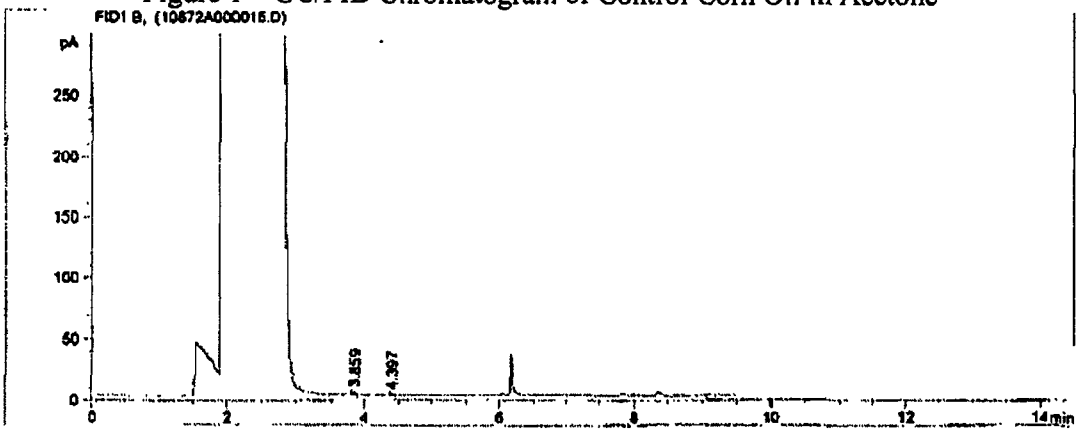
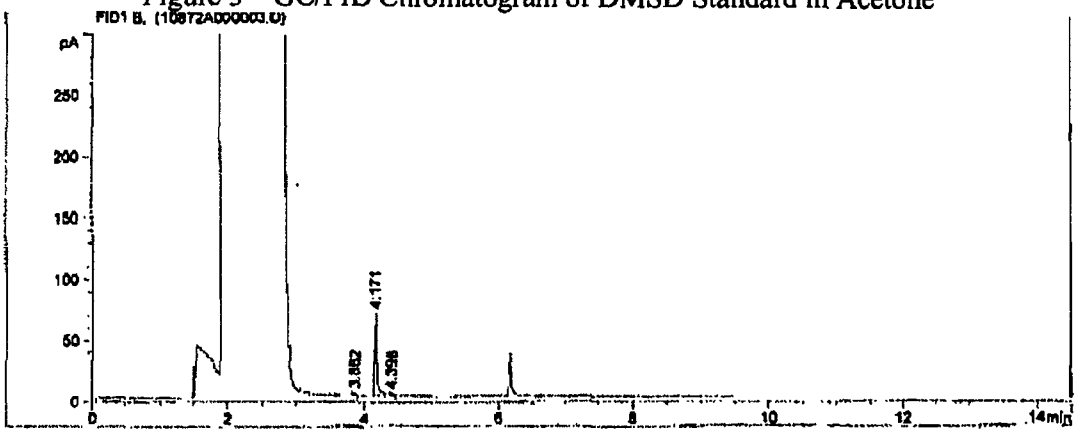



Figure 3 – GC/FID Chromatogram of DMSD Standard in Acetone



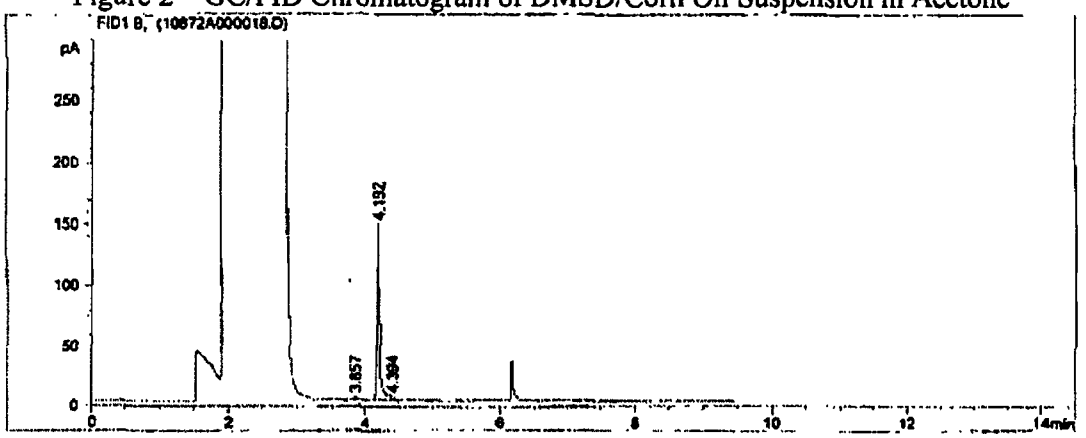


Figure 2 – GC/FID Chromatogram of DMSD/Corn Oil Suspension in Acetone